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Preparation of pharmaceuticals in a polymer matrix

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Pharmaceutical-releasing biodegradable composition comprises at least one pharmaceutical in a biodegradable polymer matrix, prepared by an ultrasonic treatment of a mixture of said polymer and said pharmaceutical (preferably an antibiotic, a steroid hormone or a polypeptide) in which said mixture is at least partially melted.

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A METHOD FOR PREPARING PHARMACEUTICAL COMPOSITIONS

The present invention relates to a method for preparing pharmaceutical compositions using ultrasonic processing.

Matrix-type drug delivery systems, which are capable of releasing pharmaceuticals in a controlled fashion over extended periods of time are well known. Drug releasing matrices have previously been prepared by conventional polymer processing techniques, such as injection molding, extrusion or compression molding. These techniques often lead to noticeable decomposition of the active agent and/or the polymer, or are slow and cumber some to use. The factors mainly responsible for their degradative effects are long heating times combined with mechanical stress caused by screws or other mixing devices in the machinery. The problems created by heat can be avoided by solvent casting, but this method may result in harmful solvent residues, and it is not suitable for insoluble polymers, such as polyglycolic acid (PGA).

It is an object of the present invention to provide a method for preparing drug releasing compositions eliminating the disad vantages discussed above. The object is realized by a method for preparing a drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix, characterized in that using ultrasonic means a mixture of the biodegradable polymer and the pharmaceutical substance is at least partially melted.

Ultrasonic techniques are widely used in industry for the joining of thermoplastic mouldings, e.g. in car and textile industry.

It has now been found that ultrasonic processing can successfully be used to plasticize and mold polymeric drug delivery systems.

Compared to the previously utilized methods, ultrasonic molding offers the advantage of being faster, more controllable, and substantially less destructive to the polymer and the drug.

Ultrasonic molding is based on a process in which energy from the main supply is converted by a generator into electrical vibrations in the US range (usually 20 kHz), and further transduced into mechanical vibrations of the same frequency. These mechanical vibrations are transmitted to the work pieces through a booster (transformer) and a sonotrode. The heating in the materials to be molded or joined takes place as a result of the absorption and reflection of the mechanical vibrations in the material and the interface friction of the fragments or joining surfaces.

The time required for ultrasonic processing is always very short, preferably less than 1.5 s. This fact is influential in all applications, particularly when mass-produced articles are in question. Short heating times are especially important in drug release applications, in which neither the polymer nor the active agent can withstand elevated temperatures for long periods of time.

Ultrasonic molding of polymer/drug composites is accomplished by standard ultrasonic welding equipment, provided it is supplied with a sonotrode and a mold suitable for producing of matrices of desired size and geometry. Tablet- or rod-shaped matrices, for example, are easily produced, but more complicated geometries can also be prepared.

Polymeric materials suitable for ultrasonically processed drug releasing matrices include e.g. polyorthoesters and biodegradable poly-a-hydroxy acids, such as polyglycolide (PGA), polylactides (PLA), polyhydroxybutyrate (PHB) and PHB/polyhydroxyvalerate (PHV) copolymers. Many of these materials are extremely difficult to injection mold or extrude due to their narrow melting temperature ranges. The process may, in fact, become impossible to control when the polymers have

been blended with pharmaceuticals: drastic changes in the viscosity of the materials can occur within a 0.5 °C change in temperature or with time, and differences in the melting points of the constituents often result in one or more of the substances being at least partially destroyed.In ultrasonic molding these problems can largely be avoided, because the process is almost instantaneous, and because the process parameters (welding time, holding time, pressure, welding energy, welding distance, amplitude, impact speed) can be very accurately determined.

Examples of the drugs compatible with ultrasonic processing are e.g. antibiotics, polypeptides and steroid hormones. Many other classes of pharmaceuticals, the long term and/or local delivery of which is beneficial, can also be used.

Ultrasonically produced drug delivery systems can best be used as macroscopic implantable devices, such as long-term contraceptive systems placed under the skin, or as antibiotic loaded rods implanted in osteomyelitic bone. The preparation of these or other types of implants consists, in general, of mixing the polymer with the pharmaceutical substances, vacuum drying the blend, and molding it with ultrasound.

Homogenization of the polymer/drug blend can be done for example by mechanically mixing finely ground powders, by stirring the polymer powder in a drug solution, by dissolving both (all) substances in a common solvent, or by impregnating the polymer with the drug solution. Thorough vacuum drying of the materials after blending is preferred for predictable processing and release results.

Molding of the materials can be done with a standard ultrasonic welding apparatus, which is equipped with an appropriately designed sonotrode and a mold of desired size and shape. The dried substances are placed into the mold, and ultrasound is applied on them. The processing time required to plasticise and form a 0.25 g sample varies between 0.1 and 1.0 s depending on the materials in question, as well as on the pressure and amplitude (booster) used.

The energies transmitted to this size of samples are approximately 50 - 500 Ws.

It has been found that most injection molded and extruded matrices show substantially worse and less predictable in vitro release behavior than ultrasonically prepared samples, which is due to the degradative effect of these methods on the polymers and especially to the drugs. In vitro drug release from ultrasonically molded samples is roughly equivalent to that from compression molded samples. However, variation of the results is greater in compression molded samples, and when comparing the processing techniques themselves, ultrasonic molding comes out as the easier, faster and more accurate technique.

The invention is further illustrated by the following
Examples, where reference is made to the accompanying drawings.

In the drawings,
Fig. 1 shows in vitro release of levonorgestrel from ultrasonically processed PLLA matrice,
Fig. 2 shows in vitro levonorgestrel release from compression molded PLLA matrice,
Fig. 3 shows in vitro ciprofloxacin release from ultrasonically molded PGA/5 wt% ciprofloxacin matrice,
Fig. 4 shows cumulative in vitro ciprofloxacin release from ultrasonically molded PGA/5 wt% ciprofloxacin m atrice,
Fig. 5 shows in vitro ciprofloxacin release from compression molded PGA/5 wt% ciprofloxacin rods, and
Fig. 6 shows in vitro ciprofloxacin release from compression molded PGA15 wt% ciprofloxacin rods.

Fig. 7 shows in vitro 1 7-B-estradiol release from ultrasonically molded PHB/PHV/7.5 wt% 17-B-estradiol slabs.

Fig. 8 shows in vitro 17- 13-estradiol release from ultrasonically molded PHB/PHV/1 5 wt% 17-B-estradiol slabs.

EXAMPLE 1.

Effects of injection molding and ultrasonic processing on poly-L-lactide (PLLA)
PLLA (MW 260 000) was first dried in vacuum and subsequently either ultrasonically processed or injection molded in nitrogen atmosphere. The samples produced by ultrasound were 0 11 x 2 mm buttons, and the duration of ultrasound application on each sample was approximately 0.3 s. The energy transmitted to the buttons was 200 Ws, and the pressure during molding 1.3 bar.

Injection molding was done with a Battenfeld BA 230 apparatus, and the molded samples were shaped as rods of various sizes. Both types of samples were ground and again vacuum dried before testing.

Processing-induced changes in polymer properties and structure were assessed by melt flow index (MFI) measurements and differential scanning calorimetry (DSC). The MFI measurements, done at 180 - 195 °C, showed that injection molding had had a major degradative effect on PLLA, as the MFI at all temperatures had markedly increased. The increase in MFI caused by ultrasonic processing was less severe (Table 1). DCS scans showed a slight decrease in melting points in the injection molded as well as in the ultrasonically processed samples. The smaller degree of crystallinity of the ultrasonically prepared PLLA is caused by the quick cooling that follows the ultrasound application (Table 2).

Table 1. Melt flow index (MFI) values of PLLA
EMI4.1

	MFI(g/IO min)			
	180°C	185°C	190°C	195°C
Raw material -	0.20	0.84	1.25	
(MW 260000)				
Injection	3.11	5.66	7.60	9.74

molded

Ultrasonically - 4.31 4.30 6.18

molded

Table 2.Melting points (°C) and degrees of crystallinity of PLLA
EMI5.1

	Tm	Crystallinity
	de	C)
Raw material	185.7	63.4
(MW260000)		
Injection molded	181.8	61.2
Ultrasonicall molded	181.1	38.9

degree of crystallinity calculated from the melting enthalpy of the sample relative to that of 100% crystalline PLLA
EXAMPLE 2.

Total concentration of active agents in ultrasonically processed, compression molded and injection molded matrices
Ultrasonically molded samples were prepared from vacuum dried PLLA (MW 260 000)/15 wt% levonorgestrel mixture using Rinco PCS ultrasonic welding equipment. The O 11 x 2 mm, button shaped samples were made using a welding time of 0.3 s, 1.3 bar and appr. 200 Ws of energy per sample. A few of the prepared samples were dissolved in chloroform, and the total concentration levonorgestrel in the solution was determined UV-spectrophotometrically at 240 nm. The levonorgestrel content of the samples was found to be close to 100% of the theoretical amount of the drug present.

A similar PLLA/15 wt% levonorgestrel mixture was compression molded into 0 20 x 2 mm slabs at 170 - 175 °C for 5 min

The pressure applied on the samples during processing was 10 M Pa.

The levonorgestrel content measured from dissolved slabs was again nearly 100% of the expected

Injection molded PLLA/15 wt% levonorgestrel samples were prepared by first melt homogenizing the dried material in a Brabender Plasticord batch mixer at 190 OC, and by then injection molding it into 0 20 x 2 mm slabs with a laboratory scale SP-2 apparatus at 195 - 200 °C. In these samples, only appr. 24 % of the theoretical amount of levonogestrel was found to be present after processing, which clearly shows the detrimental effect of injection molding / melt homogenization on these materials.

EXAMPLE 3.

In vitro release of levonogestrel from ultrasonically processed, compression molded and injection molded PLLA matrices
The in vitro hydrolysis experiments of all samples were done in phosphate buffer (pH 7.4) at 37 °C. The buffer solutions were changed periodically, and the levonorgestrel concentration in the solutions was assessed by HPLC (Merck Hitachi).

The compression molded PLLA/15% levonorgestrel matrices have released levonorgestrel fairly steadily, 10-12 Rg/day, after initial burst (Fig. 2). The release has been strongly dependent on the solubility of the steroid in the buffer solution rather than on the properties of the matrix. No signs of the active agent having been destroyed during processing have been detected, however.

The release from ultrasonically processed samples (Fig. 1) has been 6-8 ,ug/day, after the initial burst (after about 25 days).

After 180 days the total amount released has been 4.8 %.

Levonorgestrel release from the injection molded samples was barely at a detectable level (< < 1 ,eg/day) throughout most of the test period. Because of the very scant release, and also due to rapidly degrading matrices, the experiments were deemed unsuccessful and discontinued after two months of hydrolysis.

EXAMPLE 4.

In vitro ciprofloxacin release from ultrasonically processed and compression molded polyglycolic acid (PGA) matrices

Ciprofloxacin loaded PGA matrices, which can be used for the local, controlled antibiotic treatment of osteomyelitis, were prepared from ciprofloxacin impregnated Dexon 2"S" suture. The impregnated (5 wt% ciprofloxacin), vacuum dried suture was either compression molded into 0 3.2 x 5 mm rods or ultrasonically formed into 0 11 x 2 mm slabs. The compression molding was done at 200 - 205 °C under 0 - 20 MPa pressure for 6 - 7 minutes.

Ultrasonic processing was accomplished with a welding time of appr. 1.5 s, 1.2 bar pressure and 270 - 300 Ws of transmitted energy.

Ciprofloxacin release from the ultrasonically prepared samples started at 1849 + 93 ,ug/day (X+SD, N=8) and tapered down to 0.8 i 0.3 Fg/day after 112 days (Fig 3). The experiment was discontinued at this time, because all of the samples had degraded completely. At the completion of the hydrolysis the percentage of the antibiotic release had reached 55 + 5 % of its theoretical amount (Fig. 4). The remaining appr. 45 % had been lost during processing due to incomplete absorption into the

sutures.

Hydrolysis results of the compression molded samples are presented in Figures 5 and 6. It can be seen that the ciprofloxacin release from the samples was comparable to that from ultrasonically processed samples, especially considering the differences in the size and shape of the samples. However, variation between individual samples was noticeably greater in the compression molded rods. Also, the compression molding process takes 20-30 min/sample, whereas the ultrasonic forming can be done in less than two seconds.

EXAMPLE 5.

Ultrasonically molded PHB/PHV / 1 7-13-estradiol samples
Micronized estradiol and PHB/PHV powder (particle size < 350 ciam) were mechanically mixed in the ratios of 7.5 . 92.5 and 15 : 85. The homogenized mixture was vacuum dried at 30 00 for 3 days and then ultrasonically molded into 0 11 x 2 mm slabs. The processing parameters included the welding time of 0.118 - 0.128 s, 5.0 s holding time, 1.1 bar pressure and 53 Ws of welding energy.

Some of the slabs were dissolved in chioroform, and the total estradiol content of the samples was determined from the solution by a Perkin Elmer Lambda 17 UV/VIS-Spectrophotometer at 280 nm. The amount of estradiol found was close to 100 % of the theoretical.

In vitro hydrolysis experiments of PHB/PHV / 1 7-B-estradiol slabs were done in phosphate buffer (pH 7.4, 37 °C). The buffer solution was periodically changed, and the estradiol concentration in the solution was assessed by HPLC (Merck Hitachi). The results show a nearly first order release, which is typical for matrix-type drug delivery systems (Fig. 7 and 8).

Fig. 7 (mixing ratio 7.5 : 92.5) shows that the release has been 6-11 ,ug/day during the period of 20-70 days, after the initial burst. During the period of 120-290 days the release has been about 2-4 zug/day. After 290 days the total amount released has been 11.5 %.

Fig. 8 (mixing ratio 15 : 85) shows that the release has been 10-13 lig/day during the period of 50-100 days, after the initial burst. During the period of 100-230 days the release has been about 4.5-10 ,ug/day. After 230 days the total amount released has been 10.5 %.

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Claims: JP 8505076 (T)

Preparation of pharmaceuticals in a polymer matrix

Claims not available for JP 8505076 (T)
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Translate this text Claims tree

CLAIMS

1. A method for preparing a drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix, characterized in that using ultrasonic means a mixture of the biodegradable polymer and the pharmaceutical substance is at least partially melted.

2. A method according to Claim 1 characterized in that the mixture of biodegradable polymer and pharmaceutical substance is vacuum dried before the ultrasonical melting.

3. A method according to any of Claims 1-2 c h a r a c t e r i z e d in that the biodegradable polymer matrix comprises a polyorthoester, a polylactide or a poly-a-hydroxy acid

4. A method according to Claim 3 c h a r a c t e r i z e d in that the biodegradable polymer matrix comprises polyglycolide (PGA), poly-L-lactide (PLLA), polyhydroxybutyrate (PHB) or a PH B/polyhydroxyvalerate (PHV) copolymer.

5. A method according to any one of Claims 1-4 characteri z e d in that the pharmaceutical substance is an antibiotic, a steroid hormone or a polypeptide.

6. A method according to Claim 5 c h a r a c t e r i z e d in that the pharmaceutical substance is levonorgestrel, ciprofloxacin or 1 7-13-estradiol.

7. A drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix c h a r a c t e r i z e d in that said composition is prepared according any one of Claims 1-6.

8. A composition according to Claim 7 characterized in that the composition is capable of being implanted in the human or animal body.

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最終頁に続く

(54)【発明の名称】　超音波手段を用いる薬学的組成物の製造法

(57)【要約】
マトリックス型薬物送達システムを形成するために、高分子／薬物組成物を、迅速および効率的に成形することが可能である、超音波加工を用いる方法を開示する。前記方法の長所は、製造の速さおよび良好な制御である。前記方法によれば、最も常套的な製造法よりも、高分子および／または薬物の分解を引き起こすことが少なくなる。

【特許請求の範囲】

1．生体内分解性高分子マトリックスおよび該マトリックス中に混合および／または溶解される少なくとも1つの薬物からなる、薬物を放出する生体内分解性組成物の製造法であって、超音波手段を用いることにより、生体内分解性高分子および薬物の混合物が少なくとも部分的に融解することを特徴とする、薬物を放出する生体内分解性組成物の製造法。

2．生体内分解性高分子および薬物の混合物が、超音波による融解の前に真空乾燥されることを特徴とする請求の範囲第1項記載の方法。

3．生体内分解性高分子マトリックスが、ポリオルトエステル、ポリラクチドまたはポリ－α－ヒドロキシ酸からなることを特徴とする請求の範囲第1～2項のいずれかに記載の方法。

4．生体内分解性高分子マトリックスが、ポリグリコリド（ＰＧＡ）、ポリ－Ｌ－ラクチド（ＰＬＬＡ）、ポリヒドロキシ酪酸塩（ＰＨＢ）またはＰＨＢ／ポリヒドロキシ吉草酸塩（ＰＨＶ）共重合体からなることを特徴とする請求の範囲第3項記載の方法。

5．薬物が、抗生物質、ステロイドホルモンまたはポリペプチドであることを特徴とする請求の範囲第1～4項のいずれかに記載の方法。

6．薬物が、レボノルゲストレール、シプロフロキサシンまたは17－β－エストラジオールであることを特徴とする請求の範囲第5項記載の方法。

7．生体内分解性高分子マトリックスおよび該マトリッ

クス中に混合および／または溶解される少なくとも1つの薬物からなる、薬物を放出する生体内分解性組成物であって、該組成物が請求の範囲第1～6項記載のいずれかの方法により調製されることを特徴とする薬物を放出する生体内分解性組成物。

8．組成物が、人または動物の体内に移植されることが可能であることを特徴とする請求の範囲第7項記載の組成物。

【発明の詳細な説明】

超音波手段を用いる薬学的組成物の製造法

発明の分野

本発明は超音波加工を用いる薬学的組成物の製造法に関する。

発明の背景

マトリックス型の薬物送達システムは、長時間にわたる制御方式で、薬物を放出することが可能であることがよく知られている。従来では、薬物を放出するマトリックスは、射出成形、押出または圧縮成形などの一般的な高分子加工法を用いて調製されていた。これらの方法は、しばしば活性物質および／または高分子の顕著な分解を導くかまたは、時間がかかり、用いるのが面倒である。それらの分解効果の原因となるおもな要因は、機械のスクリューまたは他の混合装置によって生じる機械的な圧力に結びついた、長い加熱時間である。熱によって生じる問題は、溶剤キャスティング（solvent casting）により回避することが可能であるが、この方法によれば有害な溶剤残渣が結果として生じることがあり、ポリグリコール酸（ＰＧＡ）のような不溶性高分子には適当ではない。

発明の開示

本発明の目的は、前述の欠点を排除した、薬物を放出する組成物の製造法を提供することである。本発明の目

的は、生体内分解性高分子マトリックス、および前記マトリックス中に混合および／または溶解する少なくとも１つの薬物からなる、薬物を放出する生体内分解性組成物の製造法であって、超音波手段を用いることにより生体内分解性高分子および薬物の混合物が少なくとも部分的に融解する点を特徴とする製造法により達成される。

超音波を用いる技法は、熱可塑性成形と結びついた産業、たとえば自動車および織物産業において広く用いられている。ここで、超音波加工が高分子を用いる薬物送達システムの可塑化および成形に首尾良く用いられうることが見出された。従来用いられてきた方法と比較すると、超音波による成形法はより迅速であること、より制御可能であること、および高分子と薬物とを実質的にほとんど破壊

しないことを利点として有する。

発明を実施するための最良の形態

超音波成形は、主供給源からのエネルギーが発電機によってＵＳ域（通常２０ｋＨｚ）の電気振動に変換され、さらに同一の振動数を有する機械的な振動に変換される方法にもとづく。これらの機械的振動は増幅器（変換器）およびソノトロード（sonotrode）を通じて被加工物へ伝えられる。材料における機械的振動の吸収および反射ならびに断片もしくは接合面の境界面摩擦の結果として、成形または接合される材料が加熱される。

超音波加工に必要とされる時間は、通常きわめて短く、好ましくは１．５秒より短い。この事実は、すべての適用、とくに大量生産される製品が問題となるばあいに影響を及ぼす。加熱時間が短いことは、高分子または

活性物質のいずれもが長時間にわたる温度上昇に耐えられない、薬物放出システムへの適用においてとくに重要である。

高分子／薬物組成物の超音波成形は、所望の大きさおよび幾何学的形状のマトリックス型製剤を製造するのに適するソノロードおよび鋳型を供給するのならば、一般的な超音波溶接装置を用いて行われる。たとえば、錠剤または棒状マトリックス型製剤は、容易に生産されるだけでなく、より複雑な幾何学的形状にもまた調製することが可能である。

超音波加工される薬物放出マトリックスに適する高分子原料は、たとえばポリオルトエステル類および生体内分解性ポリ－α－ヒドロキシ酸類、たとえばポリグリコリド（ＰＧＡ）、ポリラクチド（ＰＬＡ）、ポリヒドロキシ酪酸塩（ＰＨＢ）およびＰＨＢ／ポリヒドロキシ吉草酸塩（ＰＨＶ）共重合体などが含まれる。これらの原料の多くは、それらの融解温度が狭い範囲にあるので、これらを射出成形または押出成形をすることはきわめて困難である。実際には、高分子が薬物と混合されるばあいの加工は、制御することが困難であるといってもよく、原料の粘度の急激な変化が、０．５℃の温度変化または時間とともに生じる可能性があり、成分の融点の違いにより、１つまたはより多くの物質がしばしば、少なくとも部分的に分解する結果となる。超音波加工はほとんど即時であり、加工の

パラメータ（parameter）（溶接時間、保圧（holding）時間、圧力、溶接のためのエネルギー、溶接距離、振幅、衝撃（impact）速度）がきわめて正確に測定されるので、超音波成形では、これらの問題

はほとんど回避することができる。

超音波加工に適した薬物の具体例は、たとえば抗生物質、ポリペプチド類およびステロイドホルモン類である。長期間および／または局所的な送達が有益である、ほかの多くの種類の薬物が用いられることも可能である。

超音波加工により産生される薬物送達システムは、皮下に適用される長期間の避妊システム、または骨髄炎の骨中に移植される抗生物質を充填した棒状製剤などの顕微鏡を使わず（macroscopic）に移植可能な器具として用いられるのが最良となりうる。これらの種類または他の種類の移植片の調製は、一般に薬物と高分子とを混合すること、混合物を真空乾燥することおよび超音波で成形することからなる。

高分子／薬物混合物の均質化は、たとえば微細に粉砕された粉末を機械的に混合すること、薬物溶液中で高分子粉末を撹拌すること、両（すべての）物質を一般的な溶媒中に溶解すること、または高分子に薬物溶液を含浸させることによって行うことが可能である。混合ののちに、原料を完全に真空乾燥することが、予測可能な加工をすることおよび放出効果には好ましい。

原料の成形は、適切に設計されたソノトロードおよび所望の大きさと形状の鋳型を装備する一般的な超音波溶接装置を用いて行うことが可能である。乾燥した物質を鋳型に入れ、それらに超音波を適用する。０．２５ｇのサンプルを可塑化および形成するのに必要とされる加工時間は、用いられる圧力および振幅（増幅器）と同じく、用いられる材料に依存して０．１～１．０秒の間で

変動する。この大きさのサンプルに伝えられるエネルギーは、おおよそ５０～５００Ｗｓである。

射出成形および押出成形されたほとんどのマトリックス型製剤のばあいは、超音波加工により調製されたサンプルより、in vitroにおける放出挙動が実質的に

より悪く、より予測できないことが示されており、それは高分子類およびとくに薬物に対するこれらの方法の分解効果のためであることがわかっている。超音波成形されたサンプルからのin vitroにおける薬物放出は、圧縮成形されたサンプルからの薬物放出とおよそ等しい。しかしながら、結果のばらつきは圧縮成形されたサンプルの方がより大きく、これら自体の加工方法を比較すると、超音波成形の方がより行いやすく、早く、また正確な方法であることがわかる。

本発明を、添付の図面を参照しながら以下に示す実施例によってさらに説明する。

図面の簡単な説明

図中、図１は超音波加工されたＰＬＬＡマトリックス型製剤からのレボノルゲストレール（levonorgestrel）のin vitroにおける放出を示し、図２は圧縮成形されたＰＬＬＡマトリックス型製剤からのレボノルゲストレールのin vitroにおける放出を示し、図３は超音波成形されたＰＧＡマトリックス型製剤からのシプロフロキサシン（ciprofloxacin）のin vitroにおける放出を示し、図４は超音波成形されたＰＧＡマトリックス型製剤からのシプロフロキサシンのin vitroにおける放出の累積を示し、図５は圧縮成形されたＰＧＡ棒状製剤からのシプロフロキサシンのin vitroにおける放出を示し、図６は圧縮成形されたＰＧＡ棒状製剤からのシプロフロキサシンのin vitroにおける放出の累積を示し、図７は超音波成形されたＰＨＢ／ＰＨＶ平板状製剤（７．５重量％　１７－β－エストラジオール）からの１７－β－エストラジオールのin vitroにおける放出を示し、そして図８は超音波成形されたＰＨＢ／ＰＨＶ平板状製剤（１５重量％　１７－β－エストラジオール）からの１７－β－エストラジオールのin vitroでの放出を示す。

実施例１

ポリ－Ｌ－ラクチド（poly-L-lactide）（ＰＬＬＡ）に対する射出成形および超音波加工の効果

ＰＬＬＡ（分子量２６０，０００）を、まず真空中で乾燥し、続いてチッ素雰囲気中超音波加工または射出成形のいずれかを行った。超音波によって製造され

たサンプルはφ１１×２ｍｍのボタン状であり、各サンプルに対する超音波適用の継続時間は約０．３秒であった。ボタン状の成形物に対して伝えられたエネルギーは２００Ｗｓであり、成形の間の圧力は１．３バールであった。射出成形はバッテンフェルド（Battenfeld）　ＢＡ　２３０型装置を用いて行い、成形されたサンプルを種々の大きさの棒状に形成した。両方のタイプのサンプルを試験前に研磨し、再度真空乾燥した。

加工により生じた、高分子の特性および構造における変化を、メルトフローインデックス（ＭＦＩ）の測定および示差走査熱量測定（ＤＳＣ）によって評価した。１８０～１９５℃で行われたＭＦＩ測定により、すべての

温度においてＭＦＩが顕著に増加するにつれて、射出成形はＰＬＬＡに対して目立った分解効果を有することが示された。超音波加工によって生じるＭＦＩの増加は顕著というほどではなかった（表１）。ＤＳＣ走査により、超音波加工によるサンプルと同様に、射出成形によるサンプルの融点のわずかな低下が示された。超音波適用後の急速な冷却によって、超音波加工により調製されたＰＬＬＡにより小さな結晶化度がもたらされる（表２）。

表1．PLLAのメルトフローインデックス（MFI）値

	MFI（g／10分）			
	180℃	185℃	190℃	195℃
原　料 （分子量260000）	－	0.20	0.84	1.25
射出成形	3.11	5.66	7.60	9.74
超音波成形	－	4.31	4.30	6.18

表2．PLLAの融点（℃）および結晶化度

	融点（Tm）（℃）	結晶化度（%）
原　料（分子量260000）	185.7	63.4
射出成形	181.8	61.2
超音波成形	181.1	38.9

100％結晶のPLLAの融解エンタルピーに比例するサンプルの融解エンタルピーから算出された結晶化度

実施例２

超音波加工、圧縮成形および射出成形されたマトリックス型製剤中の活性成分の総濃度

リンコ（Rinco）ＰＣＳ超音波溶接装置を用いて、真空乾燥されたＰＬＬＡ（分子量２６０，０００）／１５重量％レボノルゲストレール混合物から超音波成形されたサンプルを調製した。溶接時間０．秒、１．３バール３３およびサンプルあたりのエネルギー約２００Ｗｓを用いてφ１１×２ｍｍのボタン状のサンプルを形成した。調製されたサンプルのいくつかをクロロホルムに溶解し、溶液中の総レボノルゲストレール濃度をＵＶ－分光光度的に２４０ｎｍで測定した。サンプルのレボノルゲストレール含有量は、理論的に存在する薬物量の１００％に近いことがわかった。

同様に、ＰＬＬＡ／１５重量％レボノルゲストレール混合物を、１７０～１７５℃で５分間、φ２０×２ｍｍの平板状に圧縮成形した。加工中にサンプルに付された圧力は１０ＭＰａであった。溶解した平板状製剤から測定されたレボノルゲストレール含有量もまた、予期される含有量の１００％に近かった。

射出成形されたＰＬＬＡ／１５重量％レボノルゲストレールサンプルは、ブラベンダー　プラスチコード　バッチミキサー（Brabender Plasticord batch mixer）中、１９０℃で、乾燥した材料を最初に溶解均質化（melt homogenization）し、つぎに１９５～２００℃で実験室規模のＳＰ－２装置を用いて、φ２０×２ｍｍの平板状に射出成形することにより調製された。これらのサンプルでは、

レボノルゲストレールは理論値の約２４％しか加

工後の存在が認められず、このことは、これらの材料に対する射出成形／溶解均質化の損傷効果を明確に示している。

実施例３

超音波加工、圧縮成形および射出成形されたＰＬＬＡマトリックス型製剤からのレボノルゲストレールのin vitroにおける放出

すべてのサンプルのin vitroにおける加水分解実験をリン酸塩緩衝液（ｐＨ７．４）中、３７℃で行った。緩衝溶液を定期的に交換し、溶液中のレボノルゲストレール濃度をＨＰＬＣ（メルク（Merck）、日立（Hitachi）製）で測定した。

圧縮成形されたＰＬＬＡ／１５％レボノルゲストレールマトリックス型製剤は、最初の崩壊後１日あたり１０～１２μｇのレボノルゲストレールを顕著な程度に着実に放出した（図２）。放出は、マトリックスの特性に依存するよりもむしろ、緩衝溶液中のステロイドの溶解性に強く依存する。しかしながら、加工の間に分解された活性成分の痕跡は、検出されなかった。

超音波加工されたサンプルからの放出（図１）は、最初の崩壊後（約２５日後）、１日あたり６～８μｇである。１８０日後の総放出量は４．８％であった。

射出成形されたサンプルから放出されるレボノルゲストレールは、試験期間のほとんどを通じて、かろうじて検出できるレベル（＜＜１μｇ／日）であった。きわめてわずかな放出であるために、また急速にマトリックスを分解するために、加水分解の２ヶ月後、実験は失敗で

中断すべきと考えた。

実験例４

超音波加工および圧縮成形されたポリグリコール酸（ＰＧＡ）マトリックス型製剤から放出されるin vitroでのシプロフロキサシン

局所適用が可能であり、骨髄炎の抗生物質による治療を制御することが可能である、ＰＧＡマトリックス型製剤に含まれたシプロフロキサシンを、シプロフロキサシンを含浸したデキソン（Dexon）２“Ｓ”縫合糸から調製した。真空乾燥

された含浸（５重量％シプロフロキサシン）縫合糸をφ３．２×５ｍｍの棒状に圧縮成形するか、またはφ１１×２ｍｍの平板状に超音波成形した。圧縮成形は、２００～２０５℃、０～２０ＭＰａの圧力下で６～７分間行われた。超音波加工は、約１．５秒の溶接時間、１．２バールおよび２７０～３００Ｗｓのエネルギーを伝達することによって達成された。

超音波により調製されたサンプルからのシプロフロキサシンの放出は、１８４９±９３μｇ／日（Ｘ±標準偏差（ＳＤ）、Ｎ＝８）で始まり、１１２日後には０．８±０．３μｇ／日まで徐々に少なくなった（図３）。このときに、サンプルのすべてが完全に分解されたので、実験を中止した。加水分解の完了時における抗生物質放出の百分率は、その理論値の５５±５％まで達した（図４）。残りの約４５％は、縫合糸への不完全な吸収のために加工の間に失われた。

圧縮成形されたサンプルの加水分解の結果を、図５および６に示す。サンプルからのシプロフロキサシン放出

は、とくにサンプルの大きさおよび形の違いを考慮すると、超音波加工されたサンプルから放出されるシプロフロキサシンと同等である。しかしながら、個々のサンプル間のばらつきは、圧縮成形された棒状製剤の方が著しくより大きい。また圧縮成形加工は１サンプルあたり２０～３０分必要とするのに対し、超音波成形は２秒より短い時間で行うことができる。

実施例５

超音波成形されたＰＨＢ／ＰＨＶ／１７－β－エストラジオールサンプル

微細化されたエストラジオールおよびＰＨＢ／ＰＨＶ粉末（粉末の大きさ＜３５０μｍ）を７．５：９２．５および１５：８５の比率で機械的に混合した。均質化された混合物を３０℃で３日間、真空乾燥し、そののち、φ１１×２ｍｍ平板状に超音波成形した。加工のパラメータは、０．１１８～０．１２８秒の溶接時間、５．０秒の保圧時間、１．１バールの圧力および５３Ｗｓの溶接のためのエネルギーであった。平板状製剤のいくつかを、クロロホルムに溶解し、サンプルの総エストラジオール含量を、パーキン　エルマー　ラムダ（Perkin Elmer Lambda）１７型　ＵＶ／ＶＩＳ分光光度計を用いて２８０ｎｍで測定した。エス

トラジオールの量は、理論値の１００％に近いことがわかった。

in vitroでのＰＨＢ／ＰＨＶ／１７－β－エストラジオール平板型製剤の加水分解実験は、リン酸塩緩衝液（ｐＨ７．４、３７℃）中で行った。緩衝溶液を定期的に交換し、溶液中のエストラジオール濃度をＨＰＬＣ

（メルク、日立製）を用いて評価した。結果は、ほとんどマトリックス型薬物送達システムの典型である１次反応速度的放出を示した（図７および８）。

図７（混合比７．５：９２．５）は、最初の崩壊後の放出が２０～７０日間では６～１１μｇ／日であったことを示している。１２０～２９０日間では、放出は約２～４μｇ／日であった。２９０日後の総放出量は１１．５％であった。

図８（混合比１５：８５）は、最初の崩壊後の放出が５０～１００日間では１０～１３μｇ／日であったことを示している。１００～２３０日間では、放出は約４．５～１０μｇ／日であった。２３０日後の総放出量は１０．５％であった。

【図１】

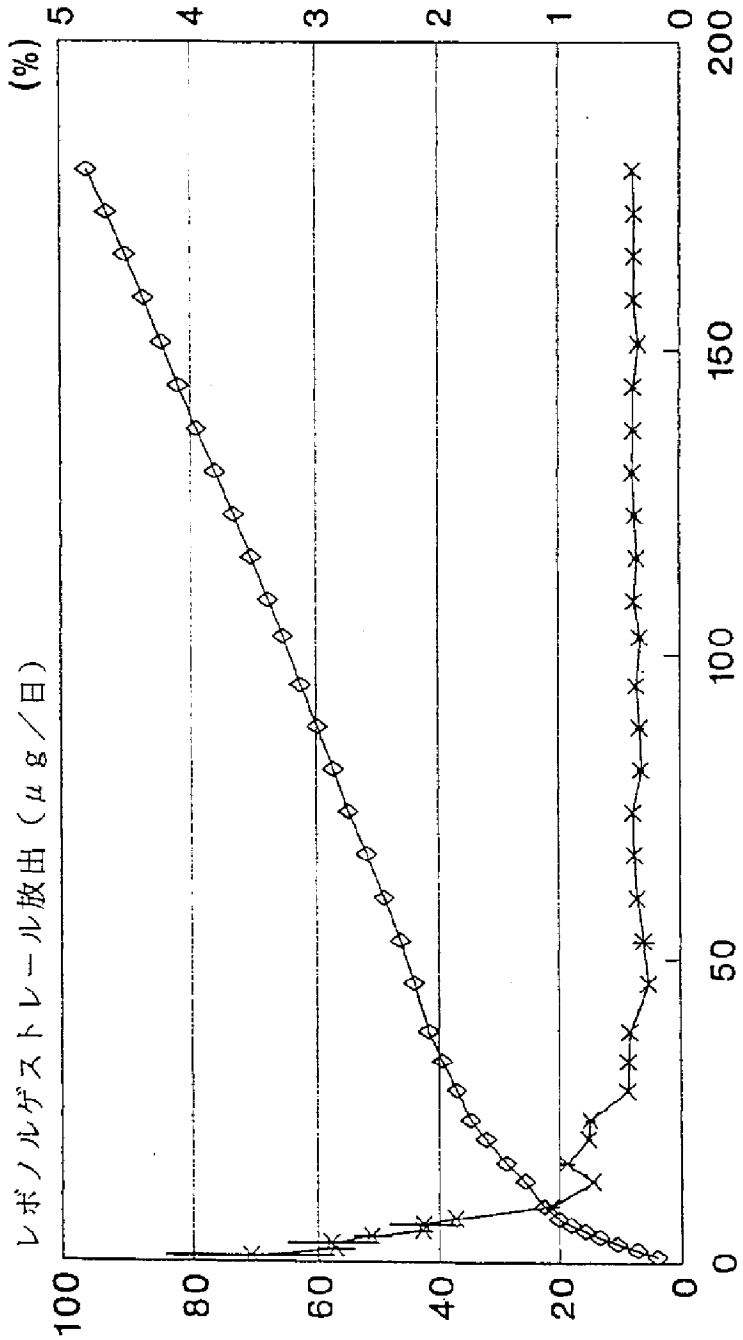

Fig. 1

【図２】

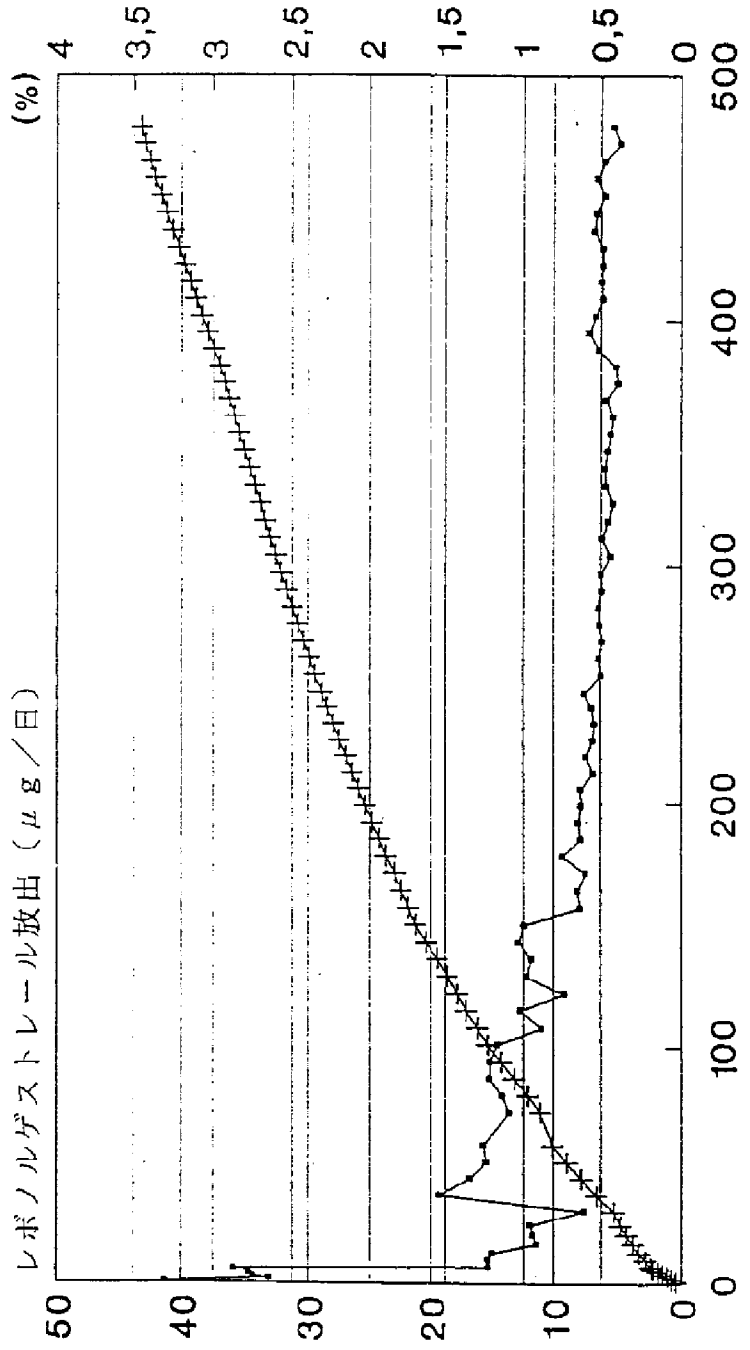
レボノルゲストレール放出（μg／日）
(%)
50
40
30
20
10
0
4
3,5
3
2,5
2
1,5
1
0,5
0
0
100
200
300
400
500
時　間（日）

Fig. 2

【図３】

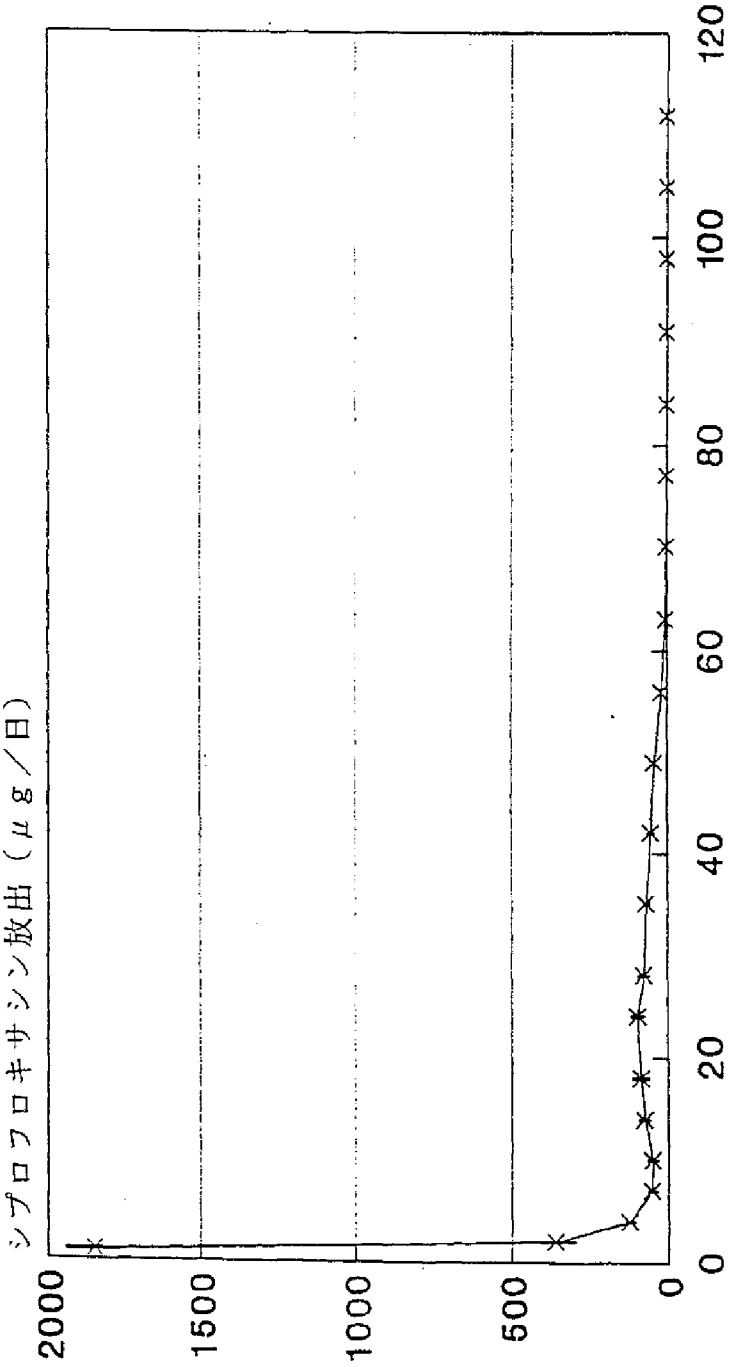

Fig. 3

【図４】

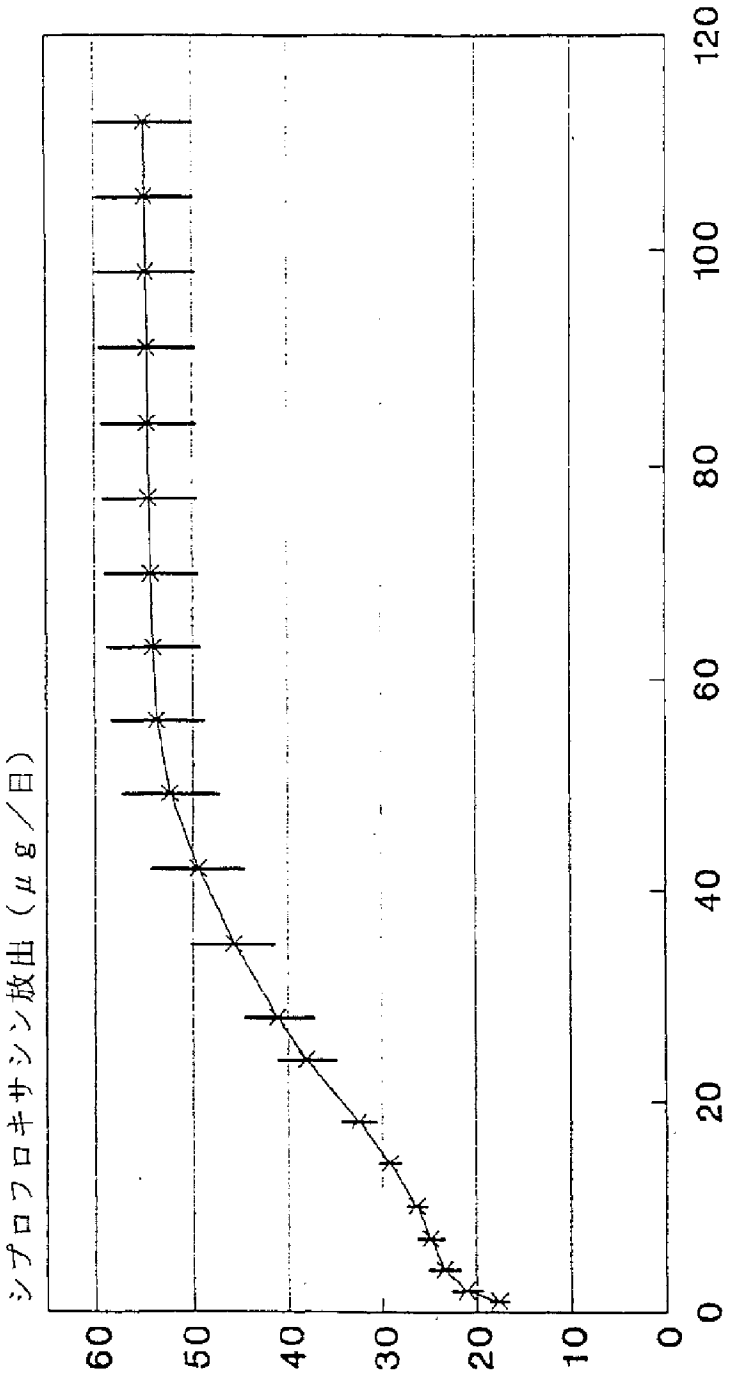

Fig. 4

【図５】

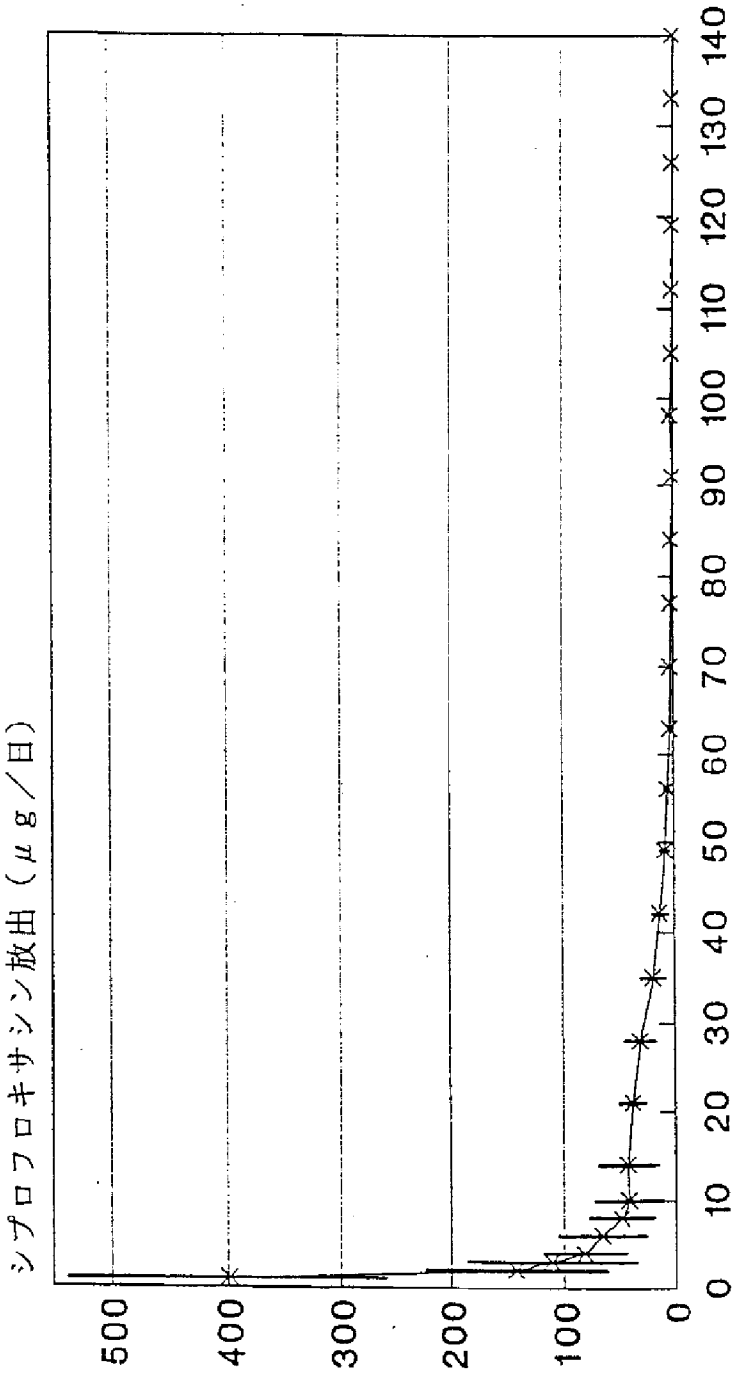
シプロフロキサシン放出（μg／日）
500
400
300
200
100
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
時　間（日）

Fig. 5

【図６】

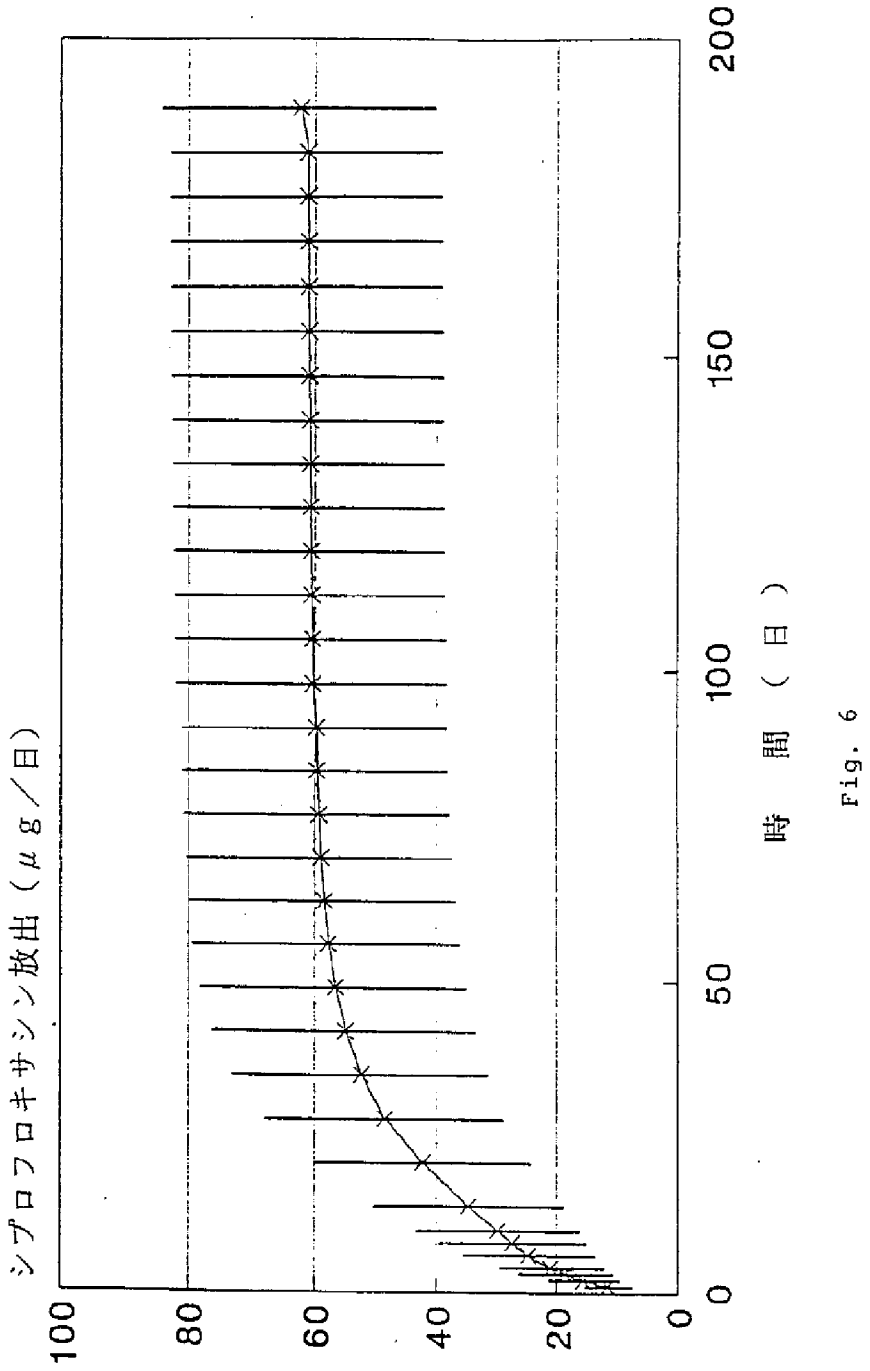

Fig. 6

【図７】

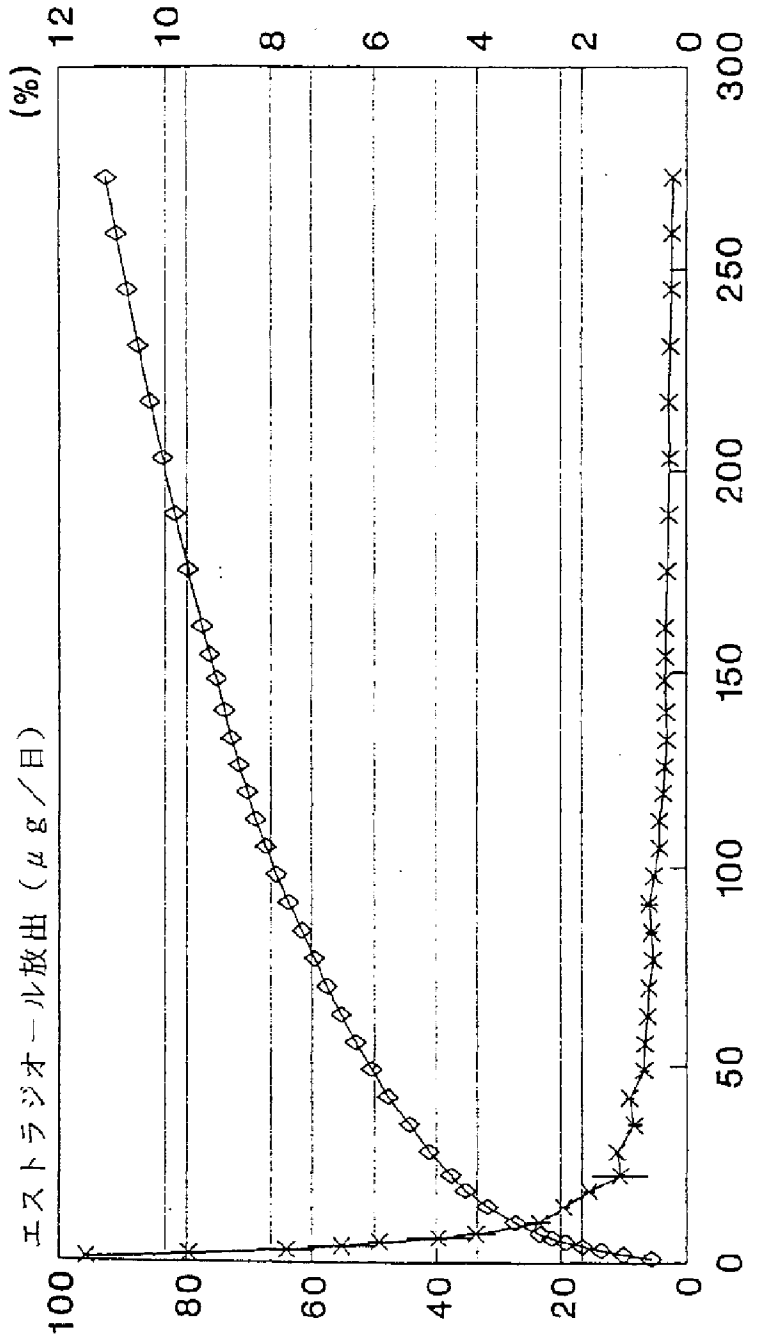
エストラジオール放出（μg／日）
(%)
100
80
60
40
20
0
12
10
8
6
4
2
0
0
50
100
150
200
250
300
時　間（日）

Fig. 7

【図８】

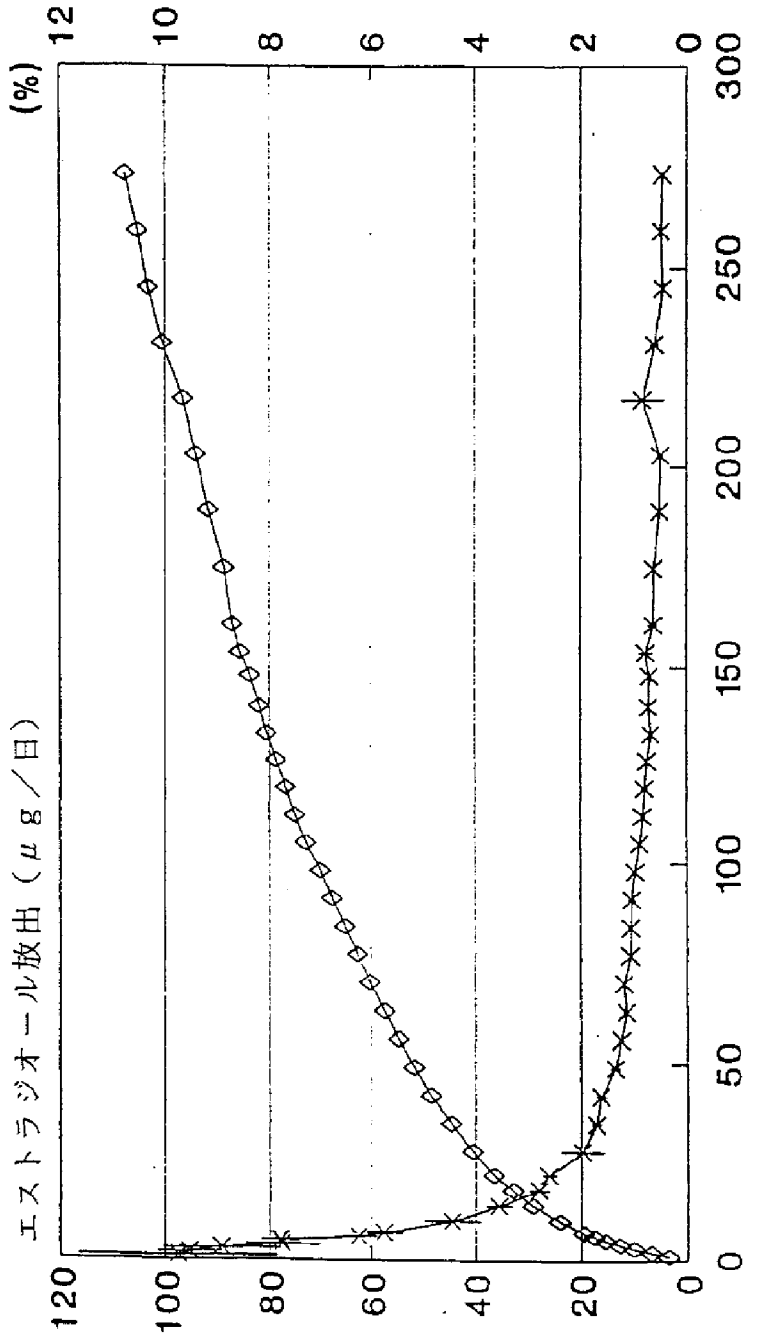
エストラジオール放出（μg／日）
(%)
120
100
80
60
40
20
0
12
10
8
6
4
2
0
0
50
100
150
200
250
300
時　間（日）

Fig. 8

【国際調査報告】

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/FI 93/00575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 556 158 (CIBA-GEIGY AG) 18 August 1993	1,5-7
P,Y	see claim 1 see column 4, line 13 - line 35 see column 5, line 37 - line 39	3,4,8
Y	EP,A,0 406 013 (ETHICON INC.) 2 January 1991 see claims 1,5,7 see column 5, line 26 - line 29	3,4,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1994	16.03.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/FI 93/00575

Pat. t document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0556158	18-08-93	US-A-	5268179	07-12-93
		AU-A-	3291093	19-08-93
		CA-A-	2089468	15-08-93
EP-A-0406013	02-01-91	US-A-	5171148	15-12-92
		CA-A-	2020076	31-12-90
		JP-A-	3068352	25-03-91

フロントページの続き

(81)指定国　　ＥＰ(ＡＴ，ＢＥ，ＣＨ，ＤＥ，ＤＫ，ＥＳ，ＦＲ，ＧＢ，ＧＲ，ＩＥ，ＩＴ，ＬＵ，ＭＣ，ＮＬ，ＰＴ，ＳＥ)，ＯＡ(ＢＦ，ＢＪ，ＣＦ，ＣＧ，ＣＩ，ＣＭ，ＧＡ，ＧＮ，ＭＬ，ＭＲ，ＮＥ，ＳＮ，ＴＤ，ＴＧ)，ＡＵ，ＢＢ，ＢＧ，ＢＲ，ＢＹ，ＣＡ，ＣＺ，ＦＩ，ＨＵ，ＪＰ，ＫＰ，ＫＲ，ＫＺ，ＬＫ，ＬＶ，ＭＧ，ＭＮ，ＭＷ，ＮＯ，ＮＺ，ＰＬ，ＲＯ，ＲＵ，ＳＤ，ＳＫ，ＵＡ，ＵＳ，ＵＺ，ＶＮ

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US005620697A

United States Patent [19]

Törmälä et al.

[11] Patent Number: 5,620,697

[45] Date of Patent: Apr. 15, 1997

[54] **METHOD FOR PREPARING MATRIX-TYPE PHARMACEUTICAL COMPOSITIONS THROUGH ULTRASONIC MEANS TO ACCOMPLISH MELTING**

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[73] Assignees: **Orion-Yhtyma Oy**, Espoo; **Leiras Oy**, Turku, both of Finland

[21] Appl. No.: **481,259**

[22] PCT Filed: **Dec. 31, 1993**

[86] PCT No.: **PCT/FI93/00575**

§ 371 Date: **Jun. 30, 1995**

§ 102(e) Date: **Jun. 30, 1995**

[87] PCT Pub. No.: **WO94/15588**

PCT Pub. Date: **Jul. 21, 1994**

[30] **Foreign Application Priority Data**

Dec. 31, 1992 [GB] United Kingdom 9227166

[51] **Int. Cl.**[6] **A61F 2/02**; A61K 47/30

[52] **U.S. Cl.** **424/426**; 514/772.3

[58] **Field of Search** 424/426; 514/772.3

[56] **References Cited**

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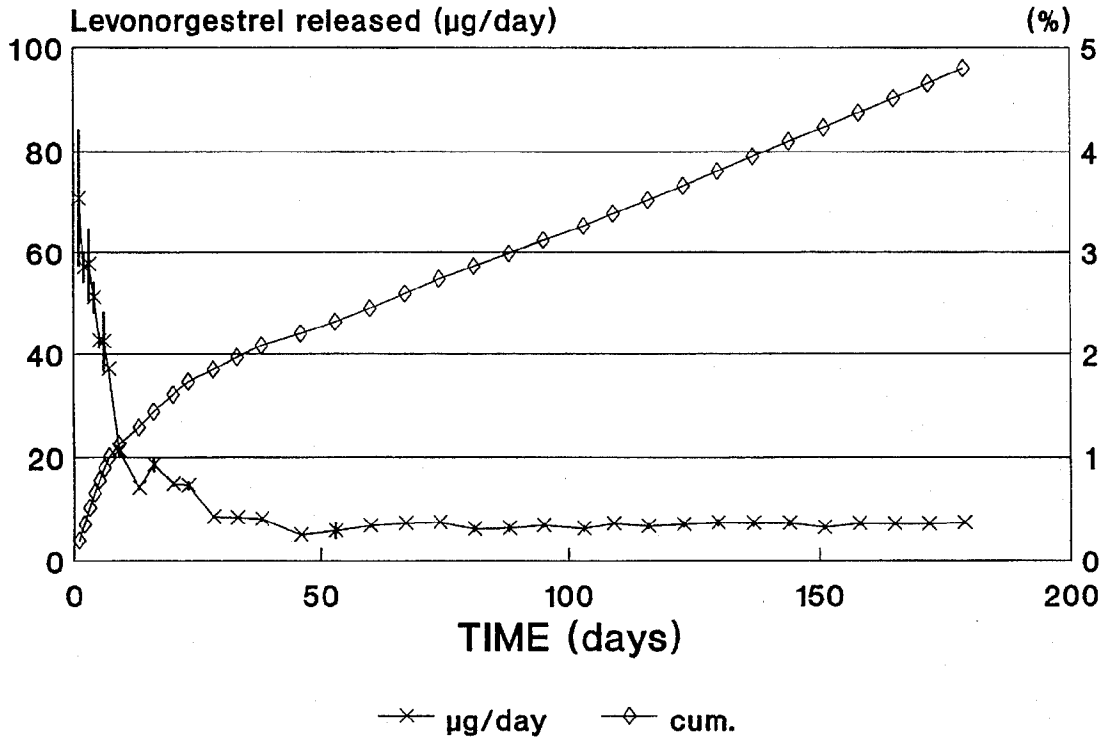
Ikada et al., *Chemical Abstracts,* vol. 116, 1991, #158947.

Primary Examiner—Carlos A. Azpuru
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

An ultrasonic processing method by which polymer/drug composites can be quickly and efficiently molded to form matrix-type drug delivery systems is disclosed. The advantages of the method include speed and good control of the process. It also causes less degradation in polymers and/or drugs than most conventional processing methods.

17 Claims, 8 Drawing Sheets



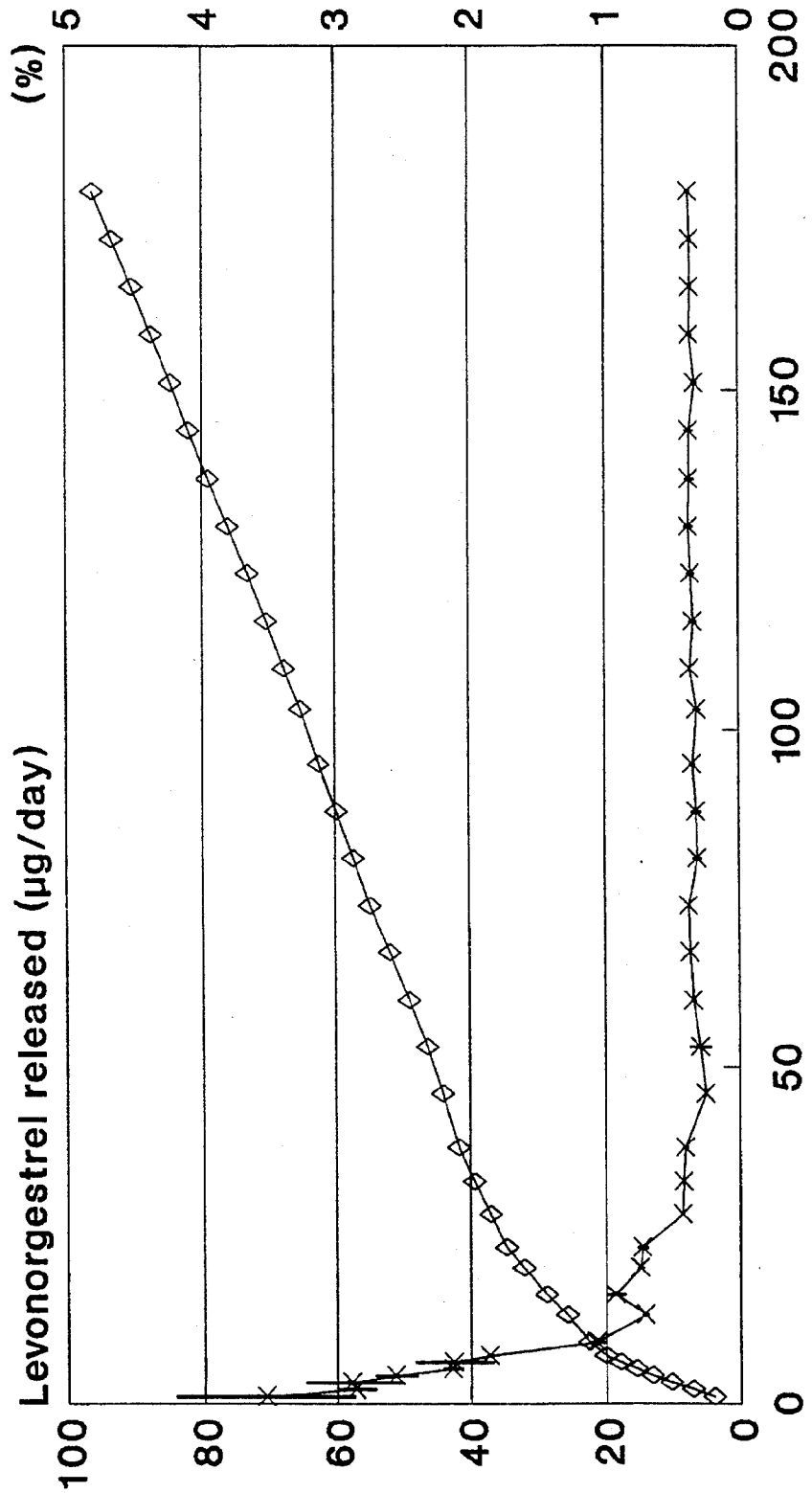

Levonorgestrel released (µg/day)
(%)
100
80
60
40
20
0
5
4
3
2
1
0
0
50
100
150
200
TIME (days)
µg/day
cum.

FIG. 1

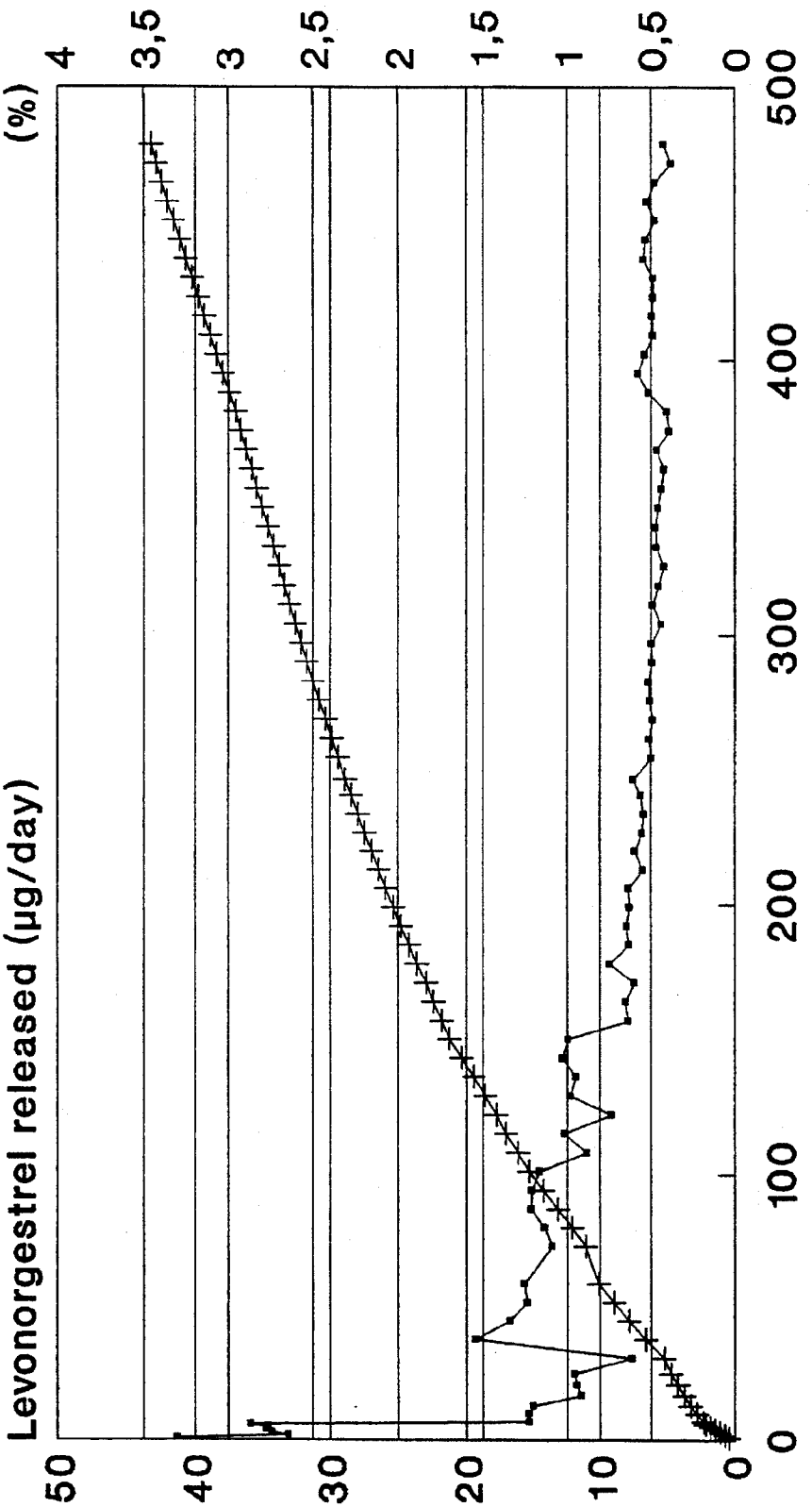

Levonorgestrel released (µg/day)
(%)
50
40
30
20
10
0
4
3,5
3
2,5
2
1,5
1
0,5
0
0
100
200
300
400
500
TIME (days)
µg/day
cum.

FIG. 2

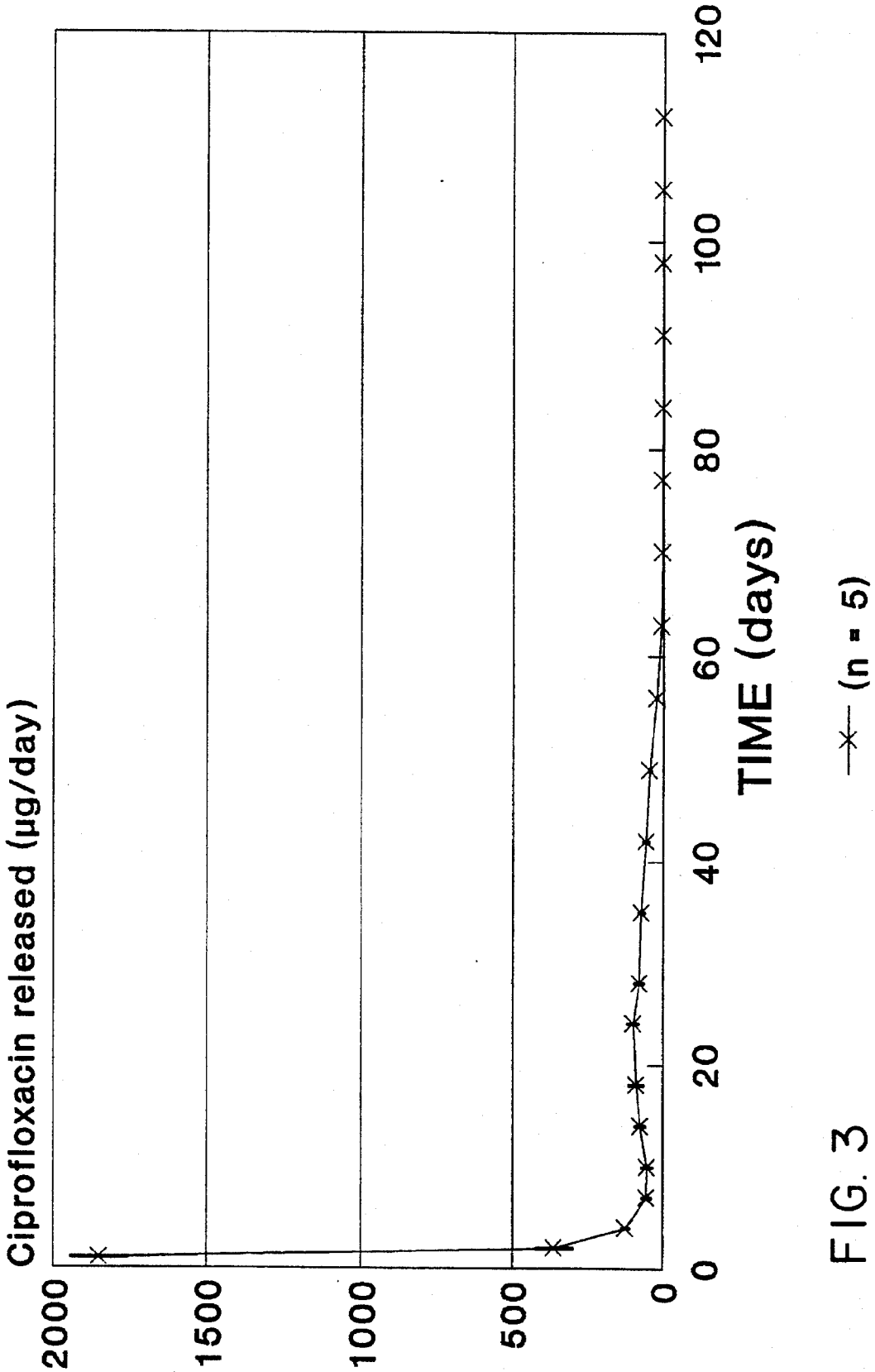

Ciprofloxacin released (µg/day)
2000
1500
1000
500
0
0
20
40
60
80
100
120
TIME (days)
(n = 5)

FIG. 3

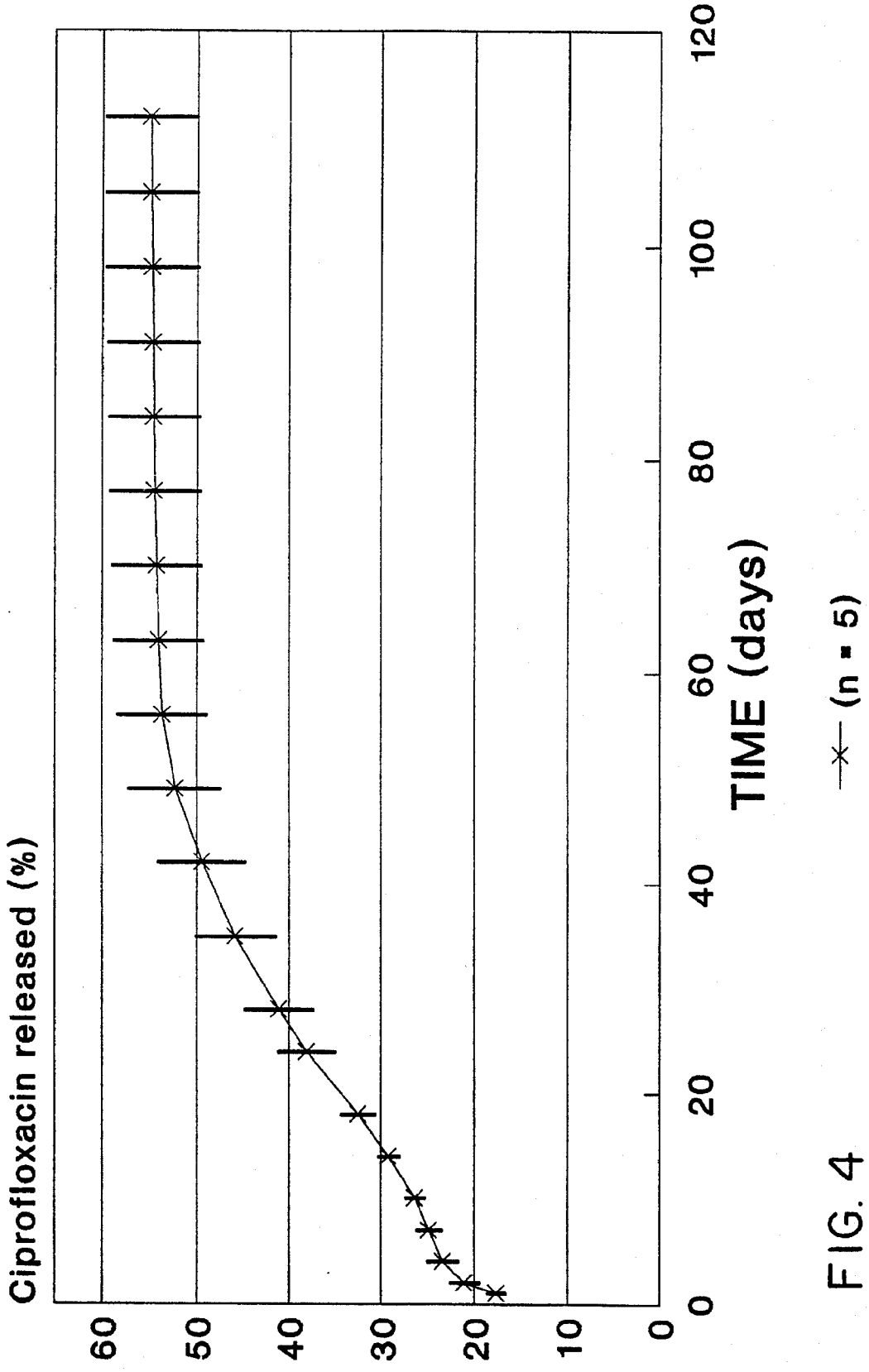

Ciprofloxacin released (%)
60
50
40
30
20
10
0
0
20
40
60
80
100
120
TIME (days)
(n = 5)

FIG. 4

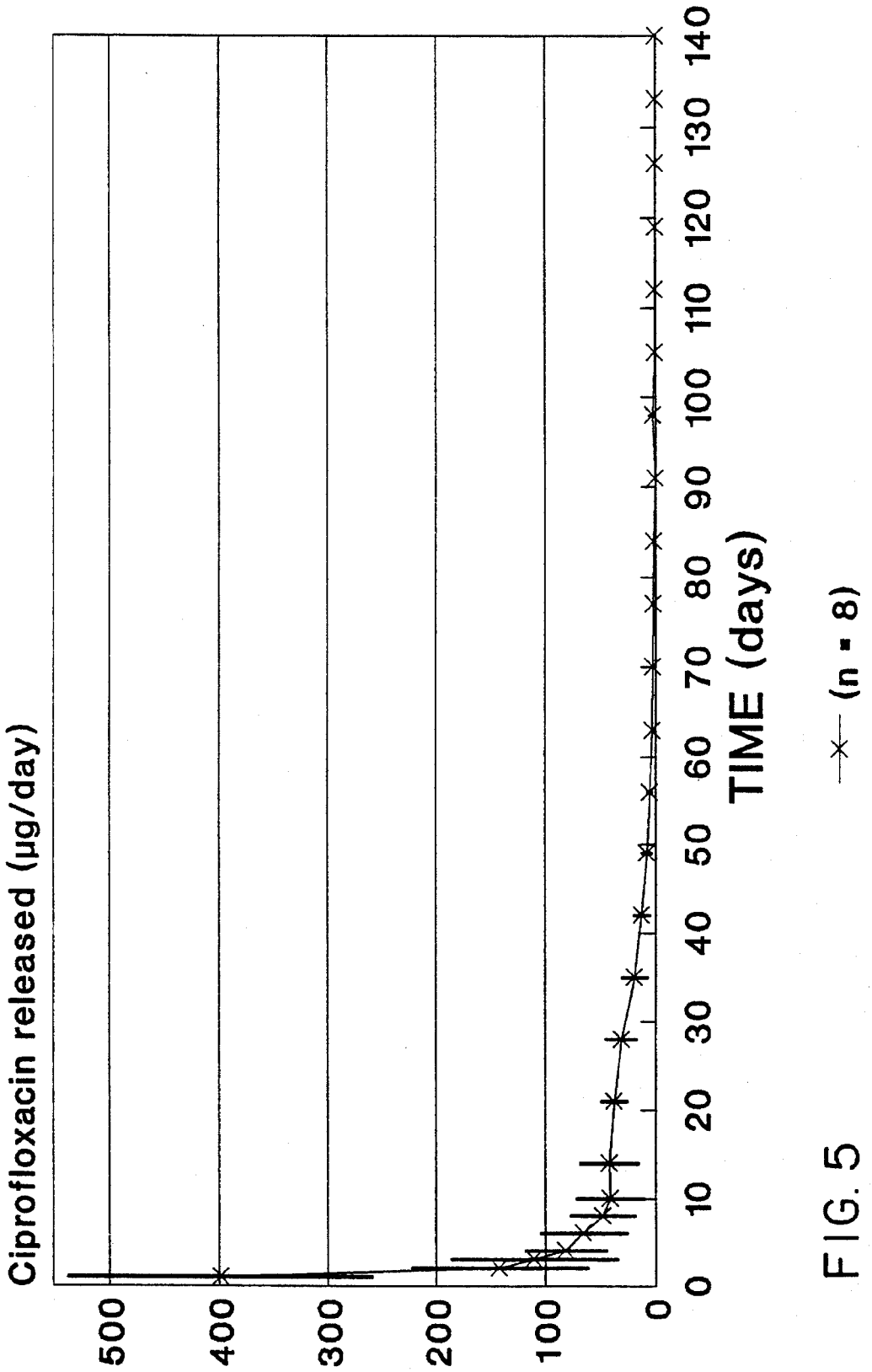

Ciprofloxacin released (µg/day)
500
400
300
200
100
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
TIME (days)
(n = 8)

FIG. 5

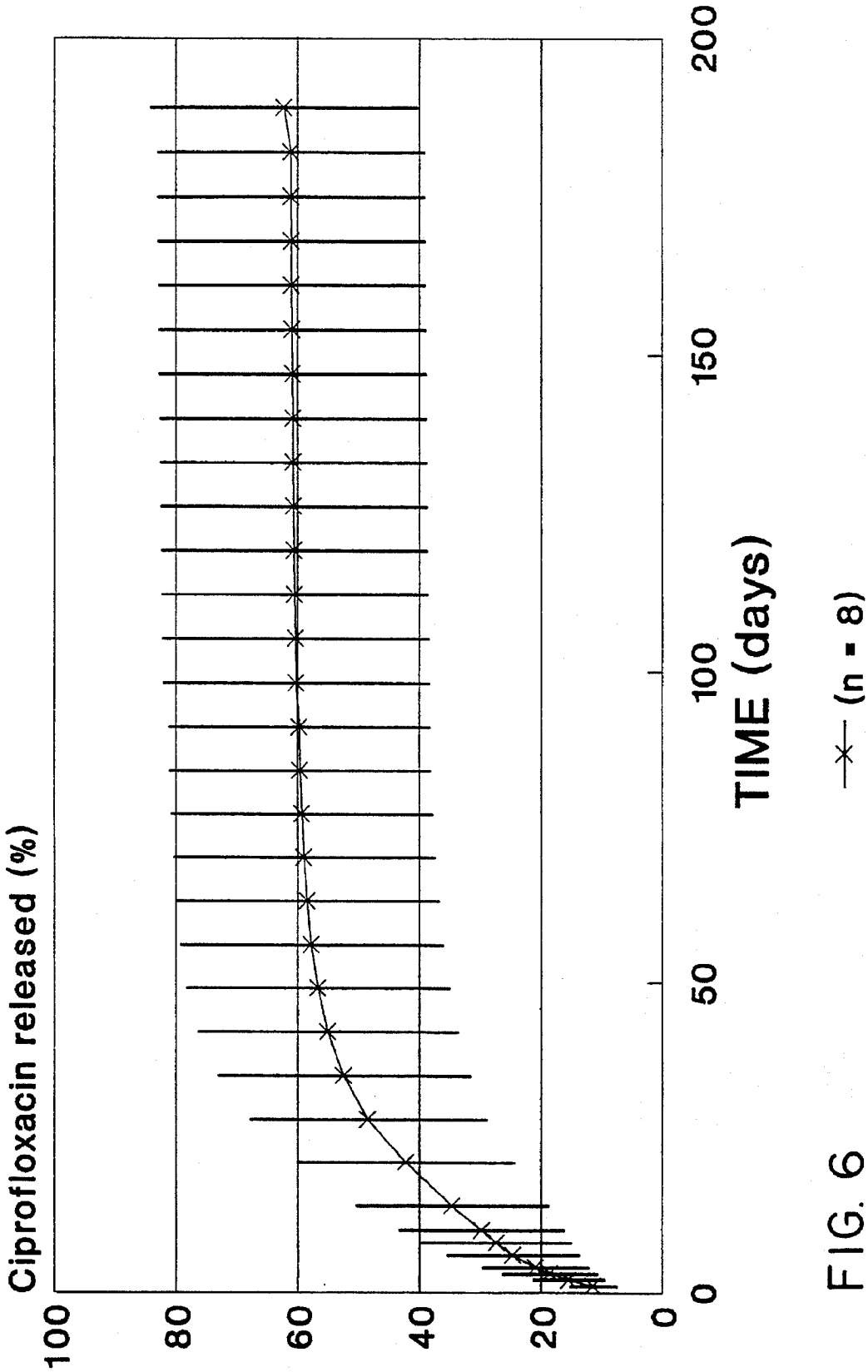

Ciprofloxacin released (%)
100
80
60
40
20
0
0
50
100
150
200
TIME (days)
(n = 8)

FIG. 6

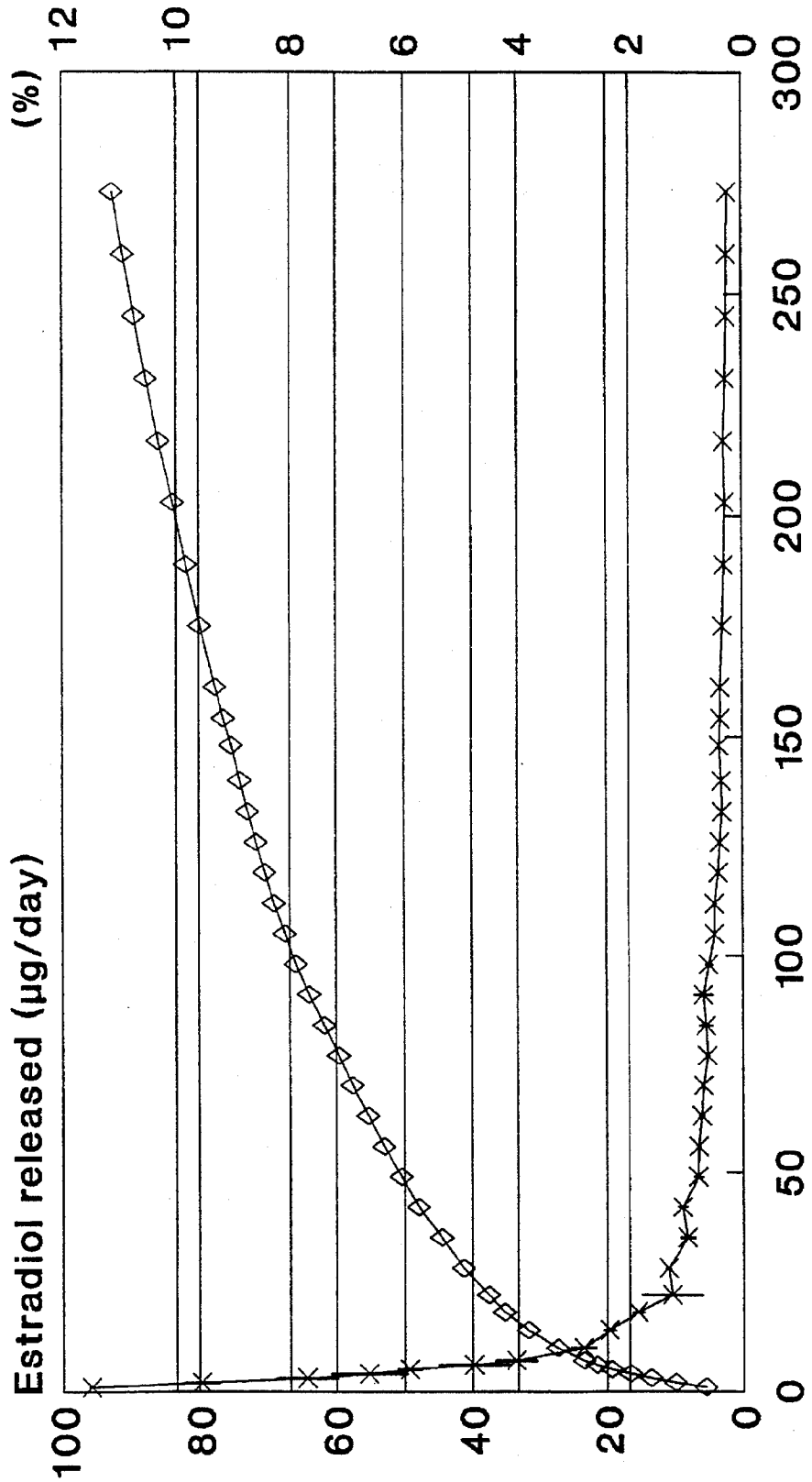

Estradiol released (µg/day)
(%)
100
80
60
40
20
0
12
10
8
6
4
2
0
0
50
100
150
200
250
300
TIME (days)
µg/day
cum.

FIG. 7

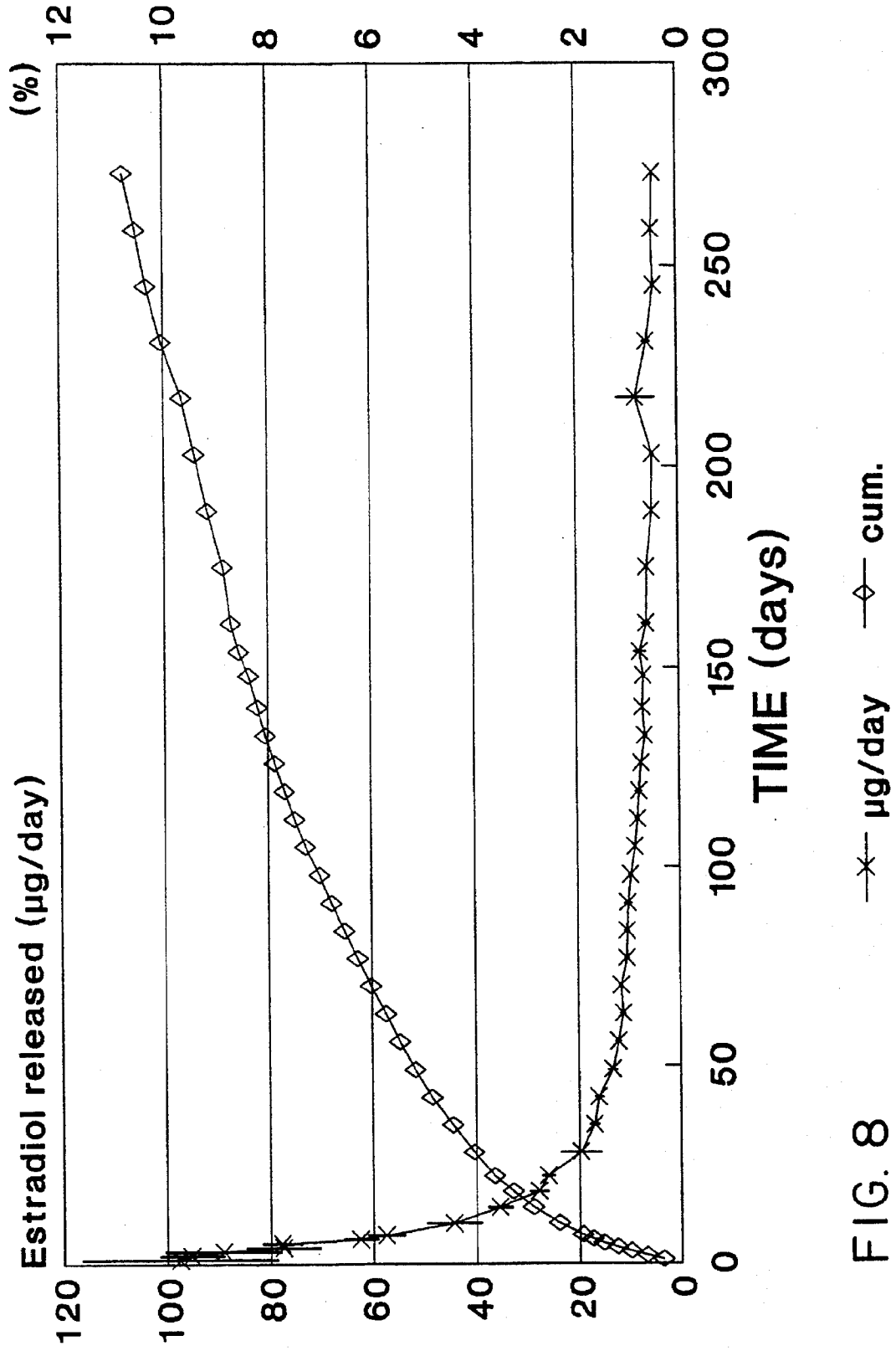

Estradiol released (µg/day)
(%)
120
100
80
60
40
20
0
12
10
8
6
4
2
0
0
50
100
150
200
250
300
TIME (days)
µg/day
cum.

FIG. 8

METHOD FOR PREPARING MATRIX-TYPE PHARMACEUTICAL COMPOSITIONS THROUGH ULTRASONIC MEANS TO ACCOMPLISH MELTING

The present invention relates to a method for preparing pharmaceutical compositions using ultrasonic processing.

Matrix-type drug delivery systems, which are capable of releasing pharmaceuticals in a controlled fashion over extended periods of time are well known. Drug releasing matrices have previously been prepared by conventional polymer processing techniques, such as injection molding, extrusion or compression molding. These techniques often lead to noticeable decomposition of the active agent and/or the polymer, or are slow and cumbersome to use. The factors mainly responsible for their degradative effects are long heating times combined with mechanical stress caused by screws or other mixing devices in the machinery. The problems created by heat can be avoided by solvent casting, but this method may result in harmful solvent residues, and it is not suitable for insoluble polymers, such as polyglycolic acid (PGA).

It is an object of the present invention to provide a method for preparing drug releasing compositions eliminating the disadvantages discussed above. The object is realized by a method for preparing a drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix, characterized in that using ultrasonic means a mixture of the biodegradable polymer and the pharmaceutical substance is at least partially melted.

Ultrasonic techniques are widely used in industry for the joining of thermoplastic moldings, e.g. in car and textile industry. It has now been found that ultrasonic processing can successfully be used to plasticize and mold polymeric drug delivery systems. Compared to the previously utilized methods, ultrasonic molding offers the advantage of being faster, more controllable, and substantially less destructive to the polymer and the drug.

Ultrasonic molding is based on a process in which energy from the main supply is converted by a generator into electrical vibrations in the US range (usually 20 kHz), and further transduced into mechanical vibrations of the same frequency. These mechanical vibrations are transmitted to the work pieces through a booster (transformer) and a sonotrode. The heating in the materials to be molded or joined takes place as a result of the absorption and reflection of the mechanical vibrations in the material and the interface friction of the fragments or joining surfaces.

The time required for ultrasonic processing is always very short, preferably less than 1.5 s. This fact is influential in all applications, particularly when mass-produced articles are in question. Short heating times are especially important in drug release applications, in which neither the polymer nor the active agent can withstand elevated temperatures for long periods of time.

Ultrasonic molding of polymer/drug composites is accomplished by standard ultrasonic welding equipment, provided it is supplied with a sonotrode and a mold suitable for producing of matrices of desired size and geometry. Tablet- or rod-shaped matrices, for example, are easily produced, but more complicated geometries can also be prepared.

Polymeric materials suitable for ultrasonically processed drug releasing matrices include e.g. polyorthoesters and biodegradable poly-α-hydroxy acids, such as polyglycolide (PGA), polylactides (PLA), polyhydroxybutyrate (PHB) and PHB/polyhydroxyvalerate (PHV) copolymers. Many of these materials are extremely difficult to injection mold or extrude due to their narrow melting temperature ranges. The process may, in fact, become impossible to control when the polymers have been blended with pharmaceuticals: drastic changes in the viscosity of the materials can occur within a 0.5° C. change in temperature or with time, and differences in the melting points of the constituents often result in one or more of the substances being at least partially destroyed. In ultrasonic molding these problems can largely be avoided, because the process is almost instantaneous, and because the process parameters (welding time, holding time, pressure, welding energy, welding distance, amplitude, impact speed) can be very accurately determined.

Examples of the drugs compatible with ultrasonic processing are e.g. antibiotics, polypeptides and steroid hormones. Many other classes of pharmaceuticals, the long term and/or local delivery of which is beneficial, can also be used.

Ultrasonically produced drug delivery systems can best be used as macroscopic implantable devices, such as long-term contraceptive systems placed under the skin, or as antibiotic loaded rods implanted in osteomyelitic bone. The preparation of these or other types of implants consists, in general, of mixing the polymer with the pharmaceutical substances, vacuum drying the blend, and molding it with ultrasound.

Homogenization of the polymer/drug blend can be done for example by mechanically mixing finely ground powders, by stirring the polymer powder in a drug solution, by dissolving both (all) substances in a common solvent, or by impregnating the polymer with the drug solution. Thorough vacuum drying of the materials after blending is preferred for predictable processing and release results.

Molding of the materials can be done with a standard ultrasonic welding apparatus, which is equipped with an appropriately designed sonotrode and a mold of desired size and shape. The dried substances are placed into the mold, and ultrasound is applied on them. The processing time required to plasticise and form a 0.25 g sample varies between 0.1 and 1.0 s depending on the materials in question, as well as on the pressure and amplitude (booster) used. The energies transmitted to this size of samples are approximately 50–500 Ws.

It has been found that most injection molded and extruded matrices show substantially worse and less predictable in vitro release behavior than ultrasonically prepared samples, which is due to the degradative effect of these methods on the polymers and especially to the drugs. In vitro drug release from ultrasonically molded samples is roughly equivalent to that from compression molded samples. However, variation of the results is greater in compression molded samples, and when comparing the processing techniques themselves, ultrasonic molding comes out as the easier, faster and more accurate technique.

The invention is further illustrated by the following Examples, where reference is made to the accompanying drawings. In the drawings,

FIG. **1** shows in vitro release of levonorgestrel from ultrasonically processed PLLA matrice,

FIG. **2** shows in vitro levonorgestrel release from compression molded PLLA matrice,

FIG. **3** shows in vitro ciprofloxacin release from ultrasonically molded PGA matrice,

FIG. **4** shows cumulative in vitro ciprofloxacin release from ultrasonically molded PGA matrice,

FIG. **5** shows in vitro ciprofloxacin release from compression molded PGA rods,

FIG. **6** shows cumulative in vitro ciprofloxacin release from compression molded PGA rods,

FIG. 7 shows in vitro 17-β-estradiol release from ultrasonically molded PHB/PHV slabs (7.5 wt % 17βestradiol) and

FIG. 8 shows in vitro 17-β-estradiol release from ultrasonically molded PHB/PHV slabs (15wt % 17-β-estradiol)

EXAMPLE 1

Effects of injection molding and ultrasonic processing on poly-L-lactide (PLLA)

PLLA (MW 260 000) was first dried in vacuum and subsequently either ultrasonically processed or injection molded in nitrogen atmosphere. The samples produced by ultrasound were ϕ 11×2 mm buttons, and the duration of ultrasound application on each sample was approximately 0.3 s. The energy transmitted to the buttons was 200 Ws, and the pressure during molding 1.3 bar. Injection molding was done with a Battenfeld BA 230 apparatus, and the molded samples were shaped as rods of various sizes. Both types of samples were ground and again vacuum dried before testing.

Processing-induced changes in polymer properties and structure were assessed by melt flow index (MFI) measurements and differential scanning calorimetry (DSC). The MFI measurements, done at 180°–195° C., showed that injection molding had had a major degradative effect on PLLA, as the MFI at all temperatures had markedly increased. The increase in MFI caused by ultrasonic processing was less severe (Table 1). DCS scans showed a slight decrease in melting points in the injection molded as well as in the ultrasonically processed samples. The smaller degree of crystallinity of the ultrasonically prepared PLLA is caused by the quick cooling that follows the ultrasound application (Table 2).

TABLE 1

Melt flow index (MFI) values of PLLA

	MFI (g/10 min) 180° C.	185° C.	190° C.	195° C.
Raw material (MW 260000)	—	0.20	0.84	1.25
Injection molded	3.11	5.66	7.60	9.74
Ultrasonically molded	—	4.31	4.30	6.18

TABLE 2

Melting points (°C.) and degrees of crystallinity of PLLA

	Tm (deg. C.)	Crystallinity %
Raw material (MW260000)	185.7	63.4
Injection molded	181.8	61.2
Ultrasonically molded	181.1	38.9

degree of crystallinity calculated from the melting enthalpy of the sample relative to that of 100% crystalline PLLA

EXAMPLE 2

Total concentration of active agents in ultrasonically processed, compression molded and injection molded matrices

Ultrasonically molded samples were prepared from vacuum dried PLLA (MW 260 000)/15 wt % levonorgestrel mixture using Rinco PCS ultrasonic welding equipment. The ϕ 11×2 mm, button shaped samples were made using a welding time of 0.3 s, 1.3 bar and appr. 200 Ws of energy per sample. A few of the prepared samples were dissolved in chloroform, and the total concentration levonorgestrel in the solution was determined UV-spectrophotometrically at 240 nm. The levonorgestrel content of the samples was found to be close to 100% of the theoretical amount of the drug present.

A similar PLLA/15 wt % levonorgestrel mixture was compression molded into ϕ 20×2 mm slabs at 170°–175° C. for 5 min. The pressure applied on the samples during processing was 10 MPa. The levonorgestrel content measured from dissolved slabs was again nearly 100% of the expected.

Injection molded PLLA/15 wt % levonorgestrel samples were prepared by first melt homogenizing the dried material in a Brabender Plasticord batch mixer at 190° C., and by then injection molding it into ϕ 20×2 mm slabs with a laboratory scale SP-2 apparatus at 195°–200° C. In these samples, only appr. 24% of the theoretical amount of levonogestrel was found to be present after processing, which clearly shows the detrimental effect of injection molding/melt homogenization on these materials.

EXAMPLE 3.

In vitro release of levonogestrel from ultrasonically processed, compression molded and injection molded PLLA matrices

The in vitro hydrolysis experiments of all samples were done in phosphate buffer (pH 7.4) at 37° C. The buffer solutions were changes periodically, and the levonorgestrel concentration in the solutions was assessed by HPLC (Merck Hitachi).

The compression molded PLLA/15% levonorgestrel matrices have released levonorgestrel fairly steadily, 10–12 μg/day, after initial burst (FIG. 2). The release has been strongly dependent on the solubility of the steroid in the buffer solution rather than on the properties of the matrix. No signs of the active agent having been destroyed during processing have been detected, however.

The release from ultrasonically processed samples (FIG. 1) has been 6–8 μg/day, after the initial burst (after about 25 days). After 180 days the total amount released has been 4.8%.

Levonorgestrel release from the injection molded samples was barely at a detectable level (<<1 μg/day) throughout most of the test period. Because of the very scant release, and also due to rapidly degrading matrices, the experiments were deemed unsuccessful and discontinued after two months of hydrolysis.

EXAMPLE 4

In vitro ciprofloxacin release from ultrasonically processed and compression molded polyglycolic acid (PGA) matrices.

Ciprofloxacin loaded PGA matrices, which can be used for the local, controlled antibiotic treatment of osteomyelitis, were prepared from ciprofloxacin impregnated Dexon 2"S" suture. The impregnated (5 wt % ciprofloxacin), vacuum dried suture was either compression molded into ϕ 3.2×5 mm rods or ultrasonically formed into ϕ 11×2 mm slabs. The compression molding was done at 200°–205° C. under 0–20 MPa pressure for 6–7 minutes. Ultrasonic processing was

accomplished with a welding time of appr. 1.5 s, 1.2 bar pressure and 270–300 Ws of transmitted energy.

Ciprofloxacin release from the ultrasonically prepared samples started at 1849±93 μg/day (X±SD, N=8) and tapered down to 0.8±0.3 μg/day after 112 days (FIG. **3**). The experiment was discontinued at this time, because all of the samples had degraded completely. At the completion of the hydrolysis the percentage of the antibiotic release had reached 55±5% of its theoretical amount (FIG. **4**). The remaining appr. 45% had been lost during processing due to incomplete absorption into the sutures.

Hydrolysis results of the compression molded samples are presented in FIGS. **5** and **6**. It can be seen that the ciprofloxacin release from the samples was comparable to that from ultrasonically processed samples, especially considering the differences in the size and shape of the samples. However, variation between individual samples was noticeably greater in the compression molded rods. Also, the compression molding process takes 20–30 min/sample, whereas the ultrasonic forming can be done in less than two seconds.

EXAMPLE 5

Ultrasonically molded PHB/PHV / 17-β-estradiol samples

Micronized estradiol and PHB/PHV powder (particle size<350 μm) were mechanically mixed in the ratios of 7.5:92.5 and 15:85. The homogenized mixture was vacuum dried at 30° C. for 3 days and then ultrasonically molded into ϕ 11×2 mm slabs. The processing parameters included the welding time of 0.118–0.128 s, 5.0 s holding time, 1.1 bar pressure and 53 Ws of welding energy. Some of the slabs were dissolved in chloroform, and the total estradiol content of the samples was determined from the solution by a Perkin Elmer Lambda 17 UV/VIS-Spectrophotometer at 280 nm. The amount of estradiol found was close to 100% of the theoretical.

In vitro hydrolysis experiments of PHB/PHV / 17-β-estradiol slabs were done in phosphate buffer (pH 7.4, 37° C.). The buffer solution was periodically changed, and the estradiol concentration in the solution was assessed by HPLC (Merck Hitachi). The results show a nearly first order release, which is typical for matrix-type drug delivery systems (FIG. **7** and **8**).

FIG. **7** (mixing ratio 7.5:92.5) shows that the release has been 6–11 μg/day during the period of 20–70 days, after the initial burst. During the period of 120–290 days the release has been about 2–4 μg/day. After 290 days the total amount released has been 11.5%.

FIG. **8** (mixing ratio 15:85) shows that the release has been 10–13 μg/day during the period of 50–100 days, after the initial burst. During the period of 100–230 days the release has been about 4.5–10 μg/day. After 230 days the total amount released has been 10.5%.

We claim:

1. A method for preparing a matrix-type solid drug releasing biodegradable composition comprising a solid biodegradable polymer matrix and at least one solid pharmaceutical substance mixed and/or dissolved within said matrix, comprising the steps of subjecting said biodegradable polymer matrix and said at least one pharmaceutical substance while in admixture as solids to the action of ultrasonic means whereby said mixture is at least partially melted, and thereafter cooling said mixture to form said matrix-type drug releasing biodegradable composition.

2. A method according to claim **1** characterized in that the mixture of biodegradable polymer and pharmaceutical substance is vacuum dried before the ultrasonical melting.

3. A method according to claim **1** characterized in that the biodegradable polymer matrix comprises a polyorthoester, a polylactide or a poly-α-hydroxy acid.

4. A method according to claim **3** characterized in that the biodegradable polymer matrix comprises polyglycolide (PGA), poly-L-lactide (PLLA), polyhydroxybutyrate (PHB) or a PHB/polyhydroxyvalerate (PHV) copolymer.

5. A method according to claim **1** characterized in that the pharmaceutical substance is an antibiotic, a steroid hormone or a polypeptide.

6. A method according to claim **5** characterized in that the pharmaceutical substance is levonorgestrel, ciprofloxacin or 17-β-estradiol.

7. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix prepared according to the method of claim **1**.

8. A matrix-type solid drug releasing biodegradable composition according to claim **7** characterized in that the composition is capable of being implanted in the human or animal body.

9. A method according to claim **2** characterized in that the biodegradable polymer matrix comprises a polyorthoester, a polylactide or a poly-α-hydroxy acid.

10. A method according to claim **2** characterized in that the pharmaceutical substance is an antibiotic, a steroid hormone or a polypeptide.

11. A method according to claim **3** characterized in that the pharmaceutical substance is an antibiotic, a steroid hormone or a polypeptide.

12. A method according to claim **4** characterized in that the pharmaceutical substance is an antibiotic, a steroid hormone or a polypeptide.

13. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix characterized in that said composition is prepared according to the method of claim **2**.

14. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix characterized in that said composition is prepared according to the method of claim **3**.

15. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix characterized in that said composition is prepared according to the method of claim **4**.

16. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix characterized in that said composition is prepared according to the method of claim **5**.

17. A matrix-type solid drug releasing biodegradable composition comprising biodegradable polymer matrix and at least one pharmaceutical substance mixed and/or dissolved within said matrix prepared according to the method of claim **6**.

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